

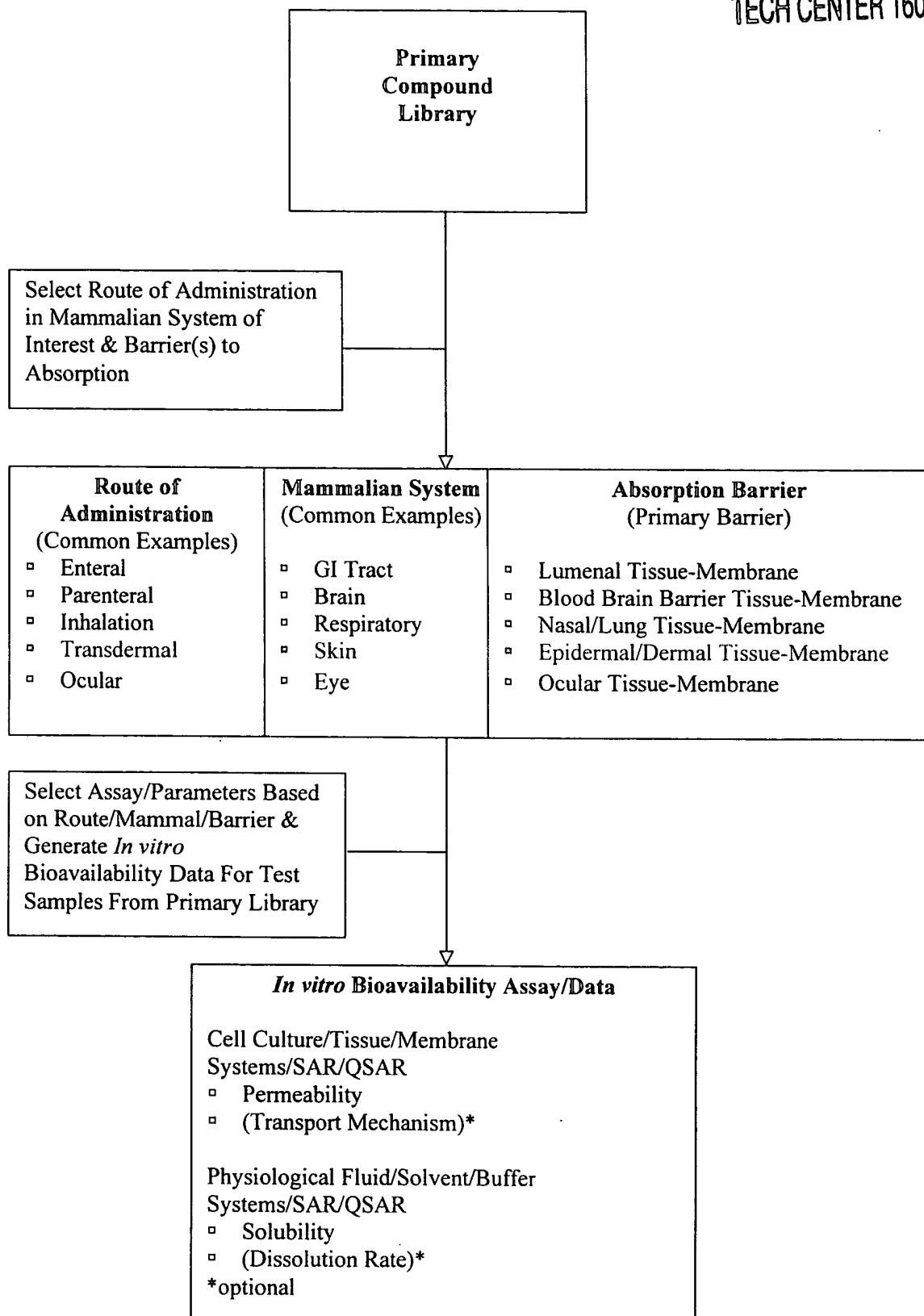


RECEIVED

MAY 05 2003

TECH CENTER 1600/2900

FIG. 1



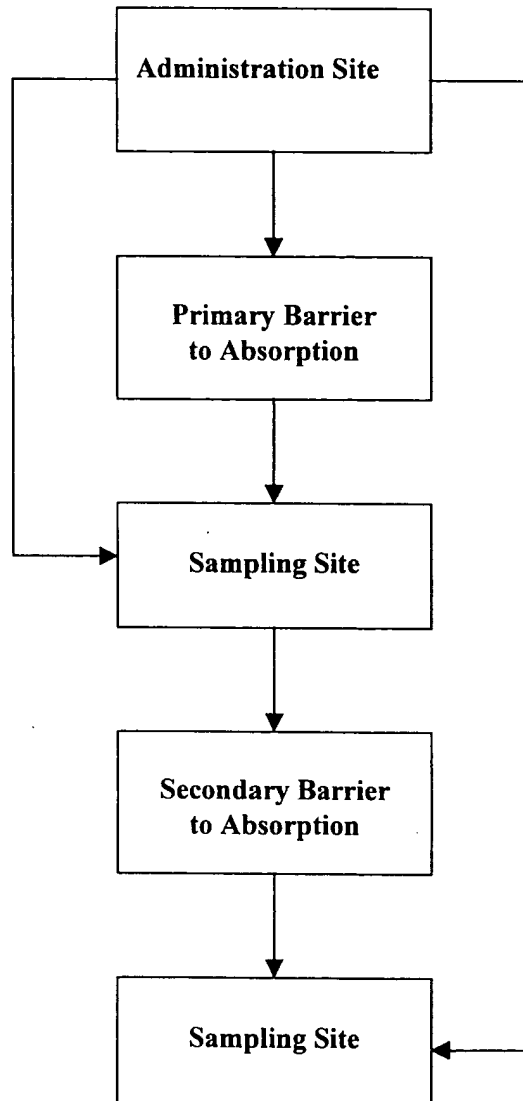


RECEIVED

MAY 05 2003

TECH CENTER 1600/2900

FIG. 2



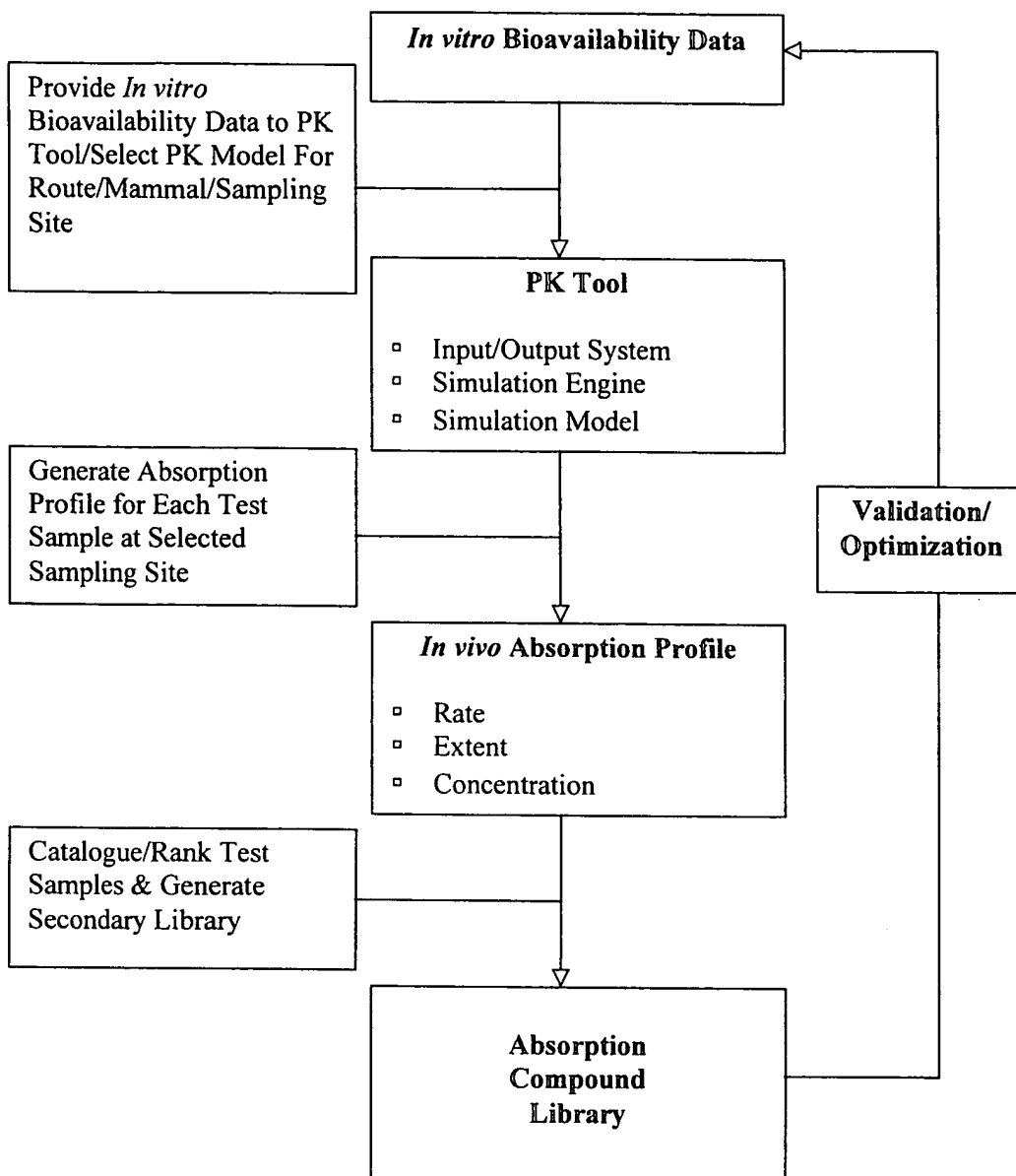


RECEIVED

MAY 05 2003

TECH CENTER 1600/2900

FIG. 3



MAY 05 2003

TECH CENTER 1600/2900

FIG. 4

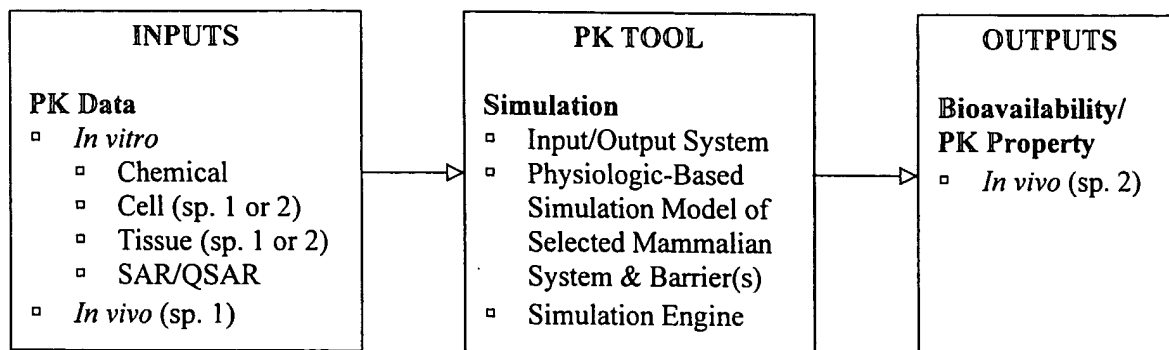
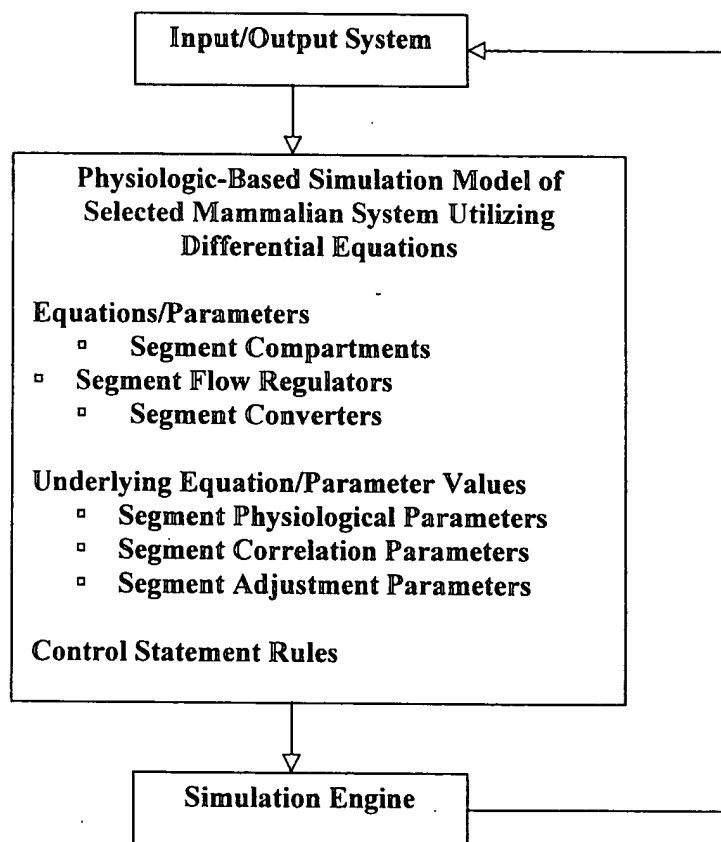


FIG. 5





RECEIVED

MAY 05 2003

TECH CENTER 1600/2900

FIG. 6

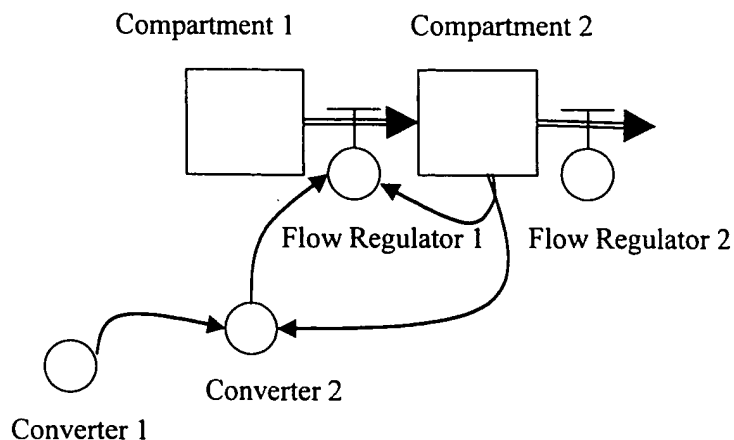

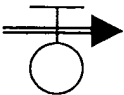




FIG. 7

Symbol	Name	Time-Dependent Function
	Compartment	Equation or value for amount of substance stored.
	Flow Regulator	Rate equation for amount of substance transferred.
	Converter	Equation or pre-defined value for (i) input into flow regulator; (ii) input into another converter; and/or (iii) storing value.
	Input Link	Directs input values.



RECEIVED

MAY 05 2003

TECH CENTER 1600/2900

FIG. 8

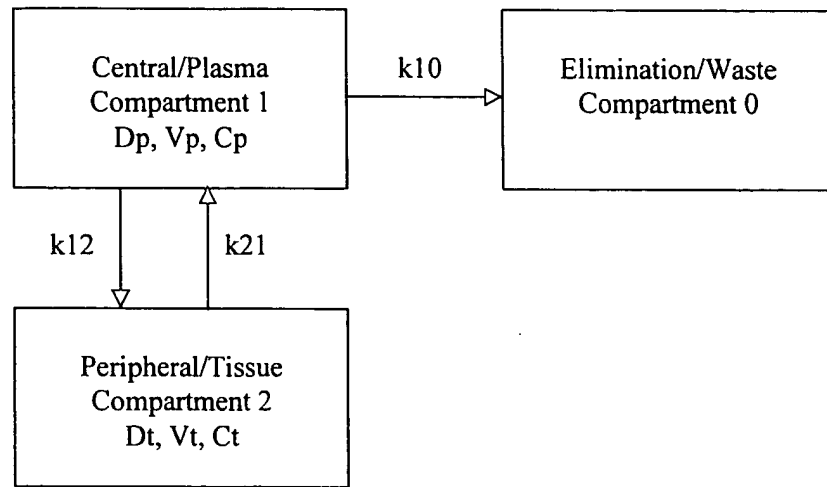
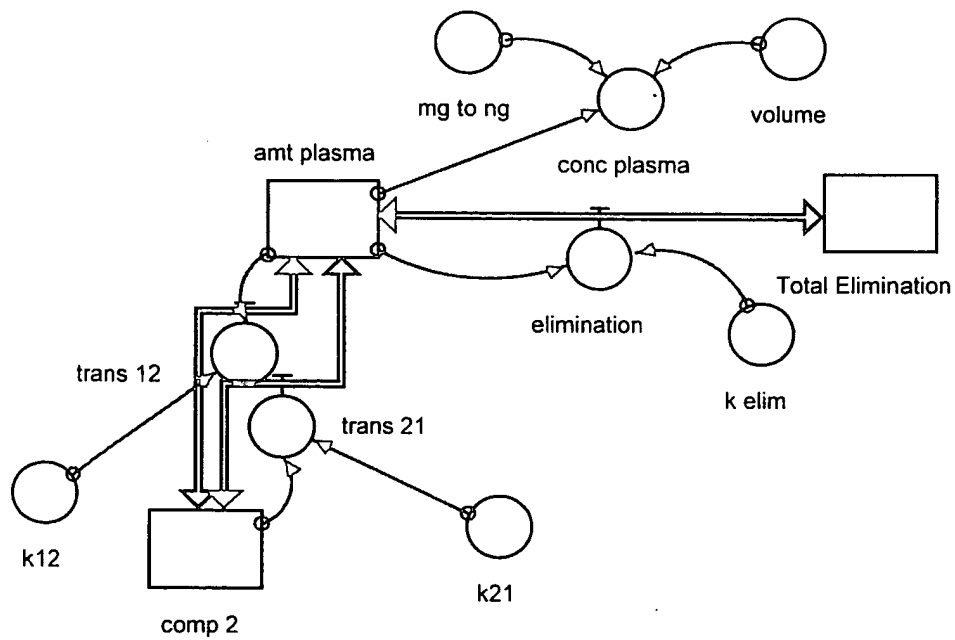


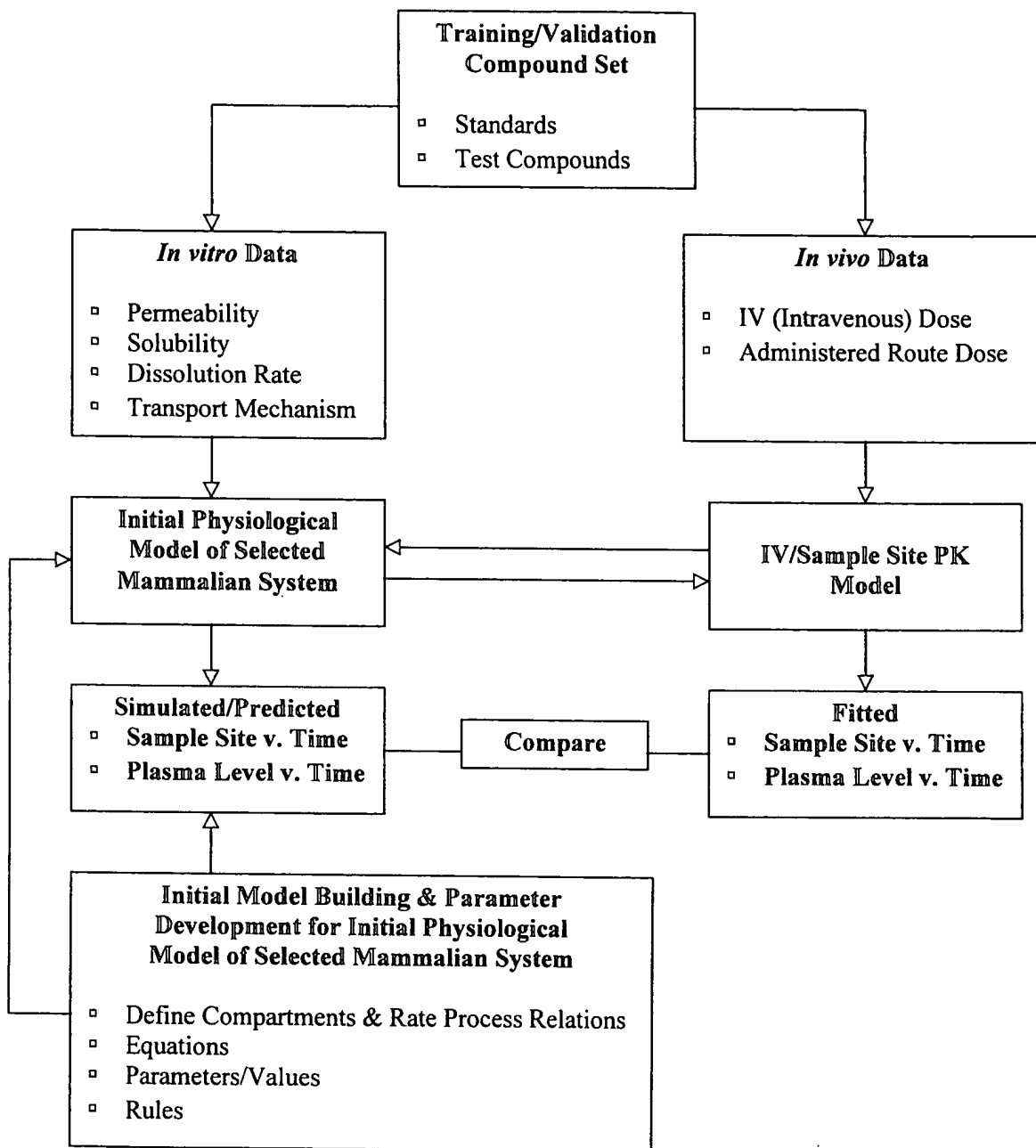
FIG. 9



MAY 05 2003

TECH CENTER 1600/2900

FIG. 10



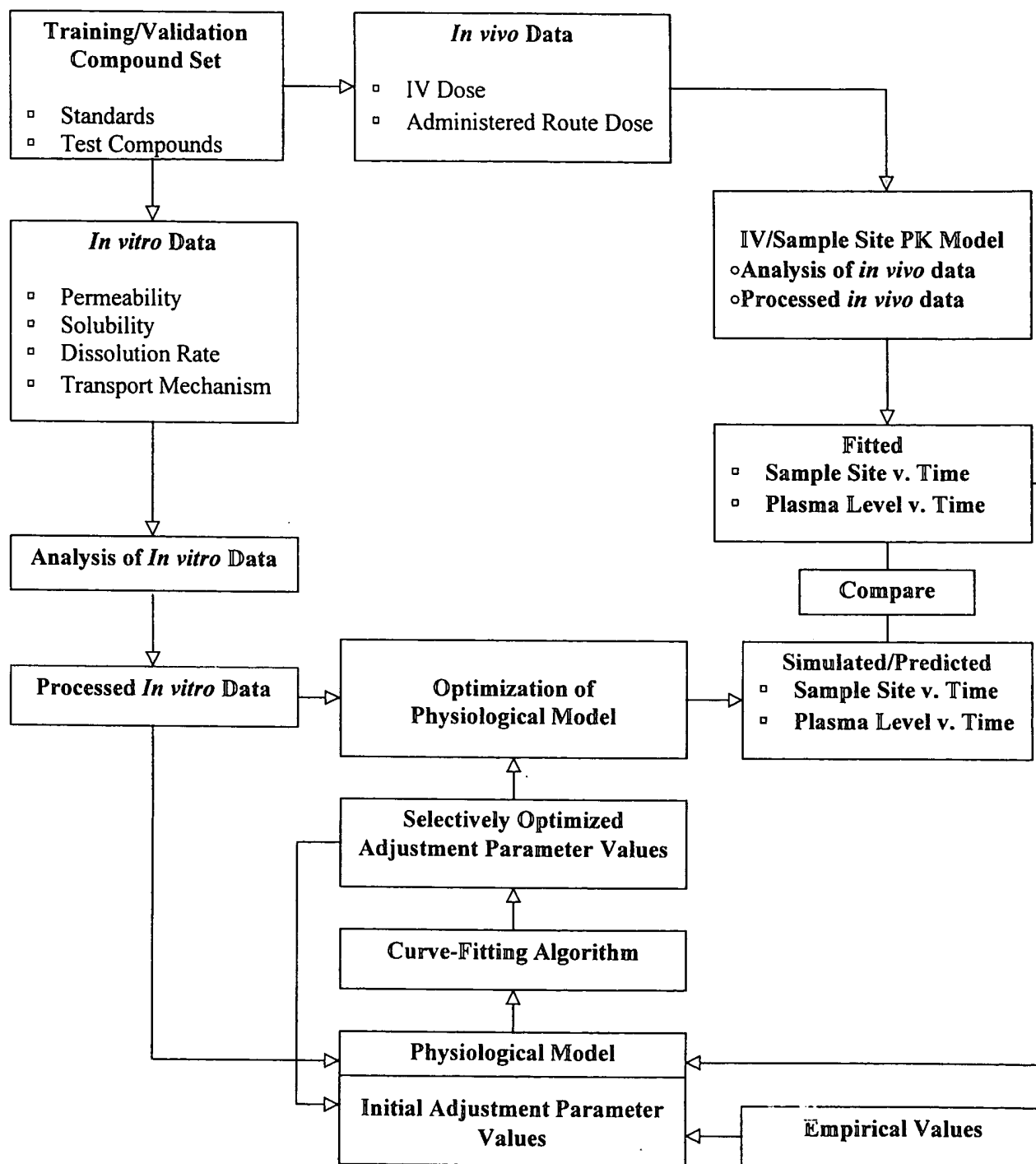


RECEIVED

MAY 05 2003

TECH CENTER 1600/2900

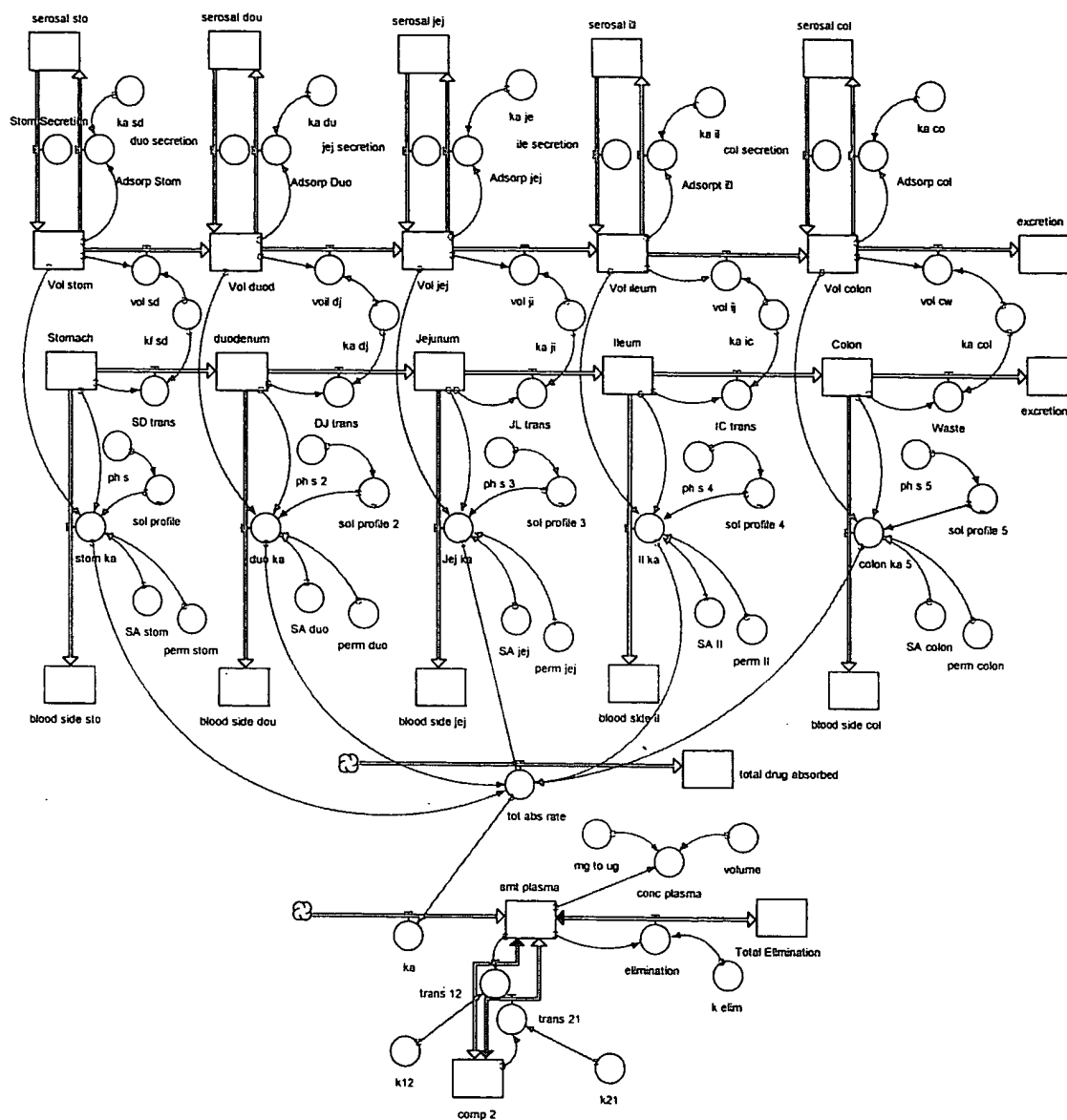
FIG. 11



MAY 05 2003

TECH CENTER 1600/2900

FIG. 12





RECEIVED

MAY 05 2003

TECH CENTER 1600/2900

FIG. 13

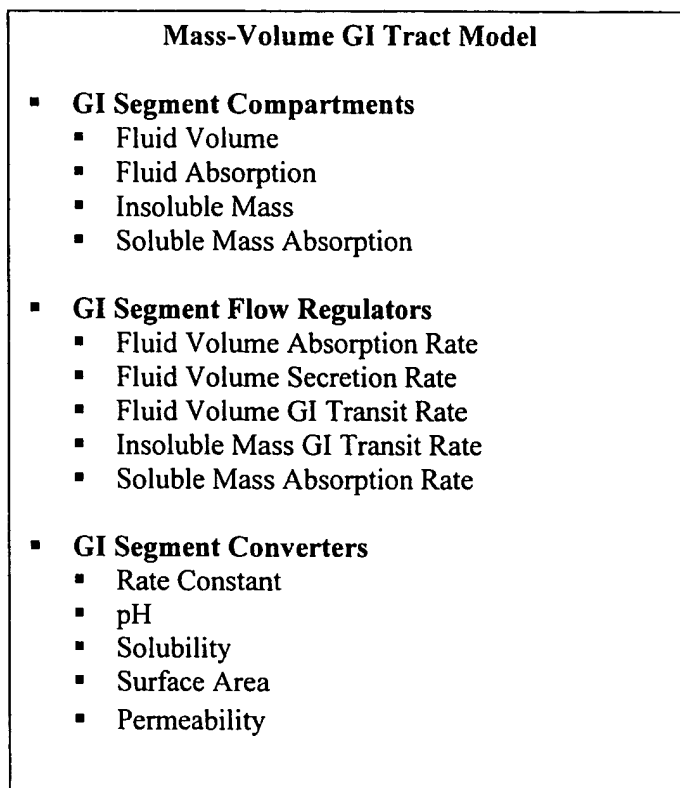
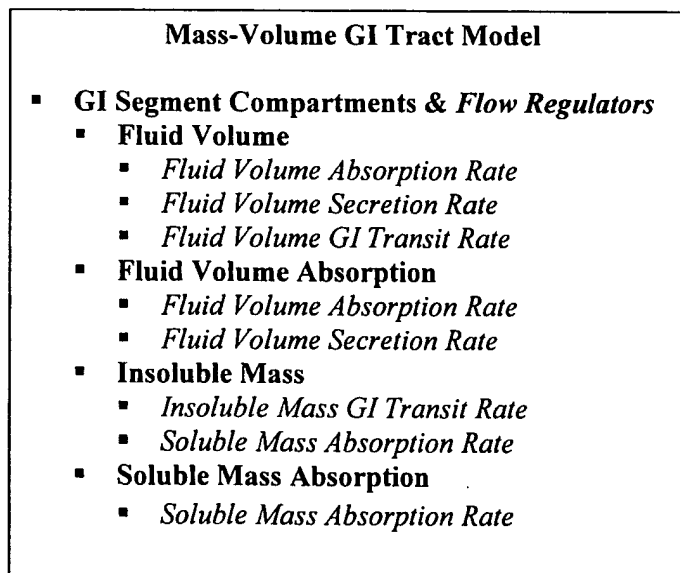


FIG. 14





RECEIVED

MAY 05 2003

FIG. 15

TECH CENTER 1600/2900

Mass-Volume GI Tract Model

- **GI Segment Flow Regulators & Converters**
 - **Fluid Volume Absorption Rate**
 - *Fluid Volume Absorption Rate Constant*
 - **Fluid Volume Secretion Rate**
 - *Fluid Volume Secretion Rate Constant*
 - **Fluid Volume GI Transit Rate**
 - *Fluid Volume GI Transit Rate Constant*
 - **Insoluble Mass GI Transit Rate**
 - *Insoluble Mass GI Transit Rate Constant*
 - **Soluble Mass Absorption Rate**
 - *Fluid Volume*
 - *Insoluble Mass*
 - *Mass Solubility Profile*
 - *pH*
 - *Permeability*
 - *Surface Area*

FIG. 16

Mass-Volume GI Tract Model

- **GI Segment Converters**
 - *Rate Constant*
 - *pH*
 - *Solubility*
 - *Surface Area*
 - *Permeability*



RECEIVED

MAY 05 2003

TECH CENTER 1600/2900

FIG. 17

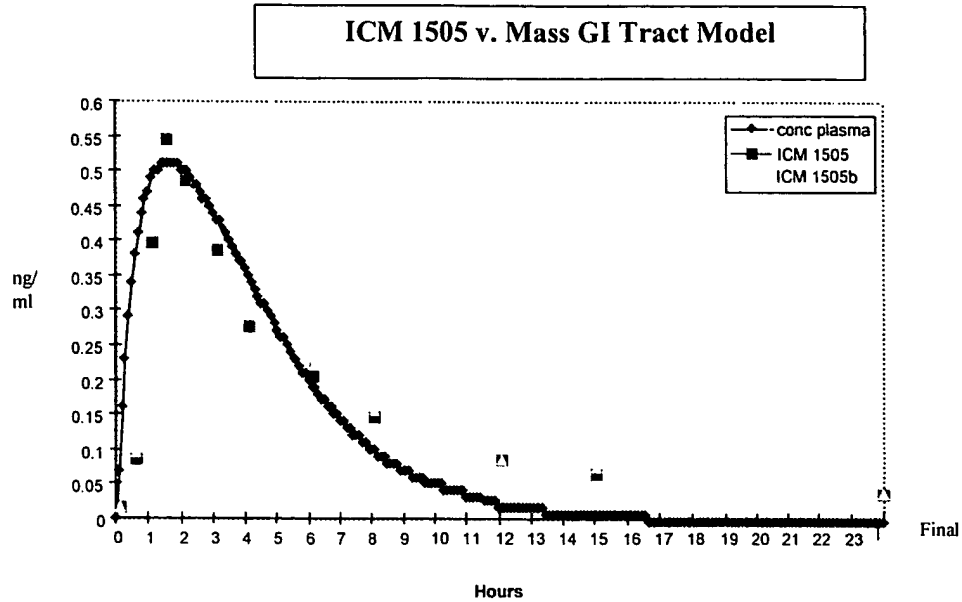
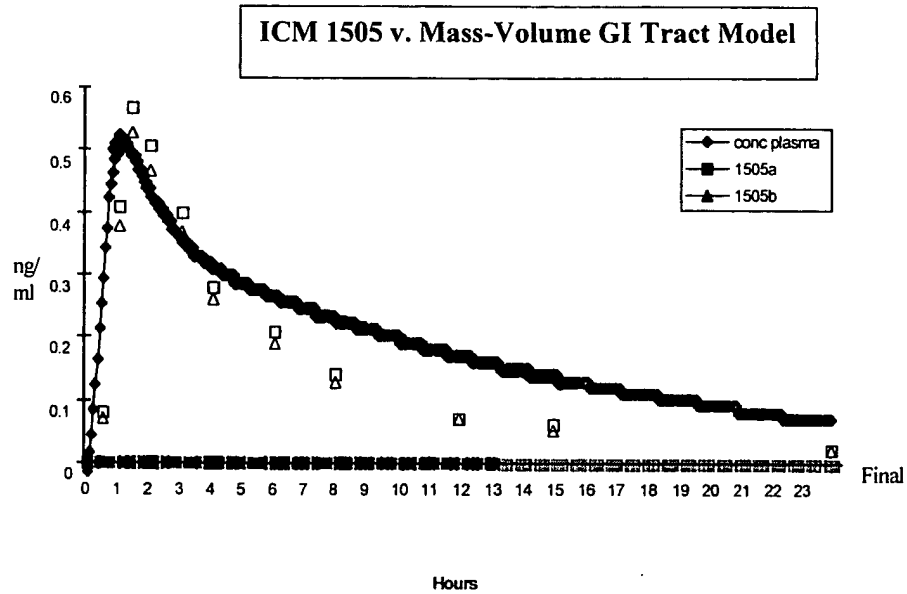


FIG. 18



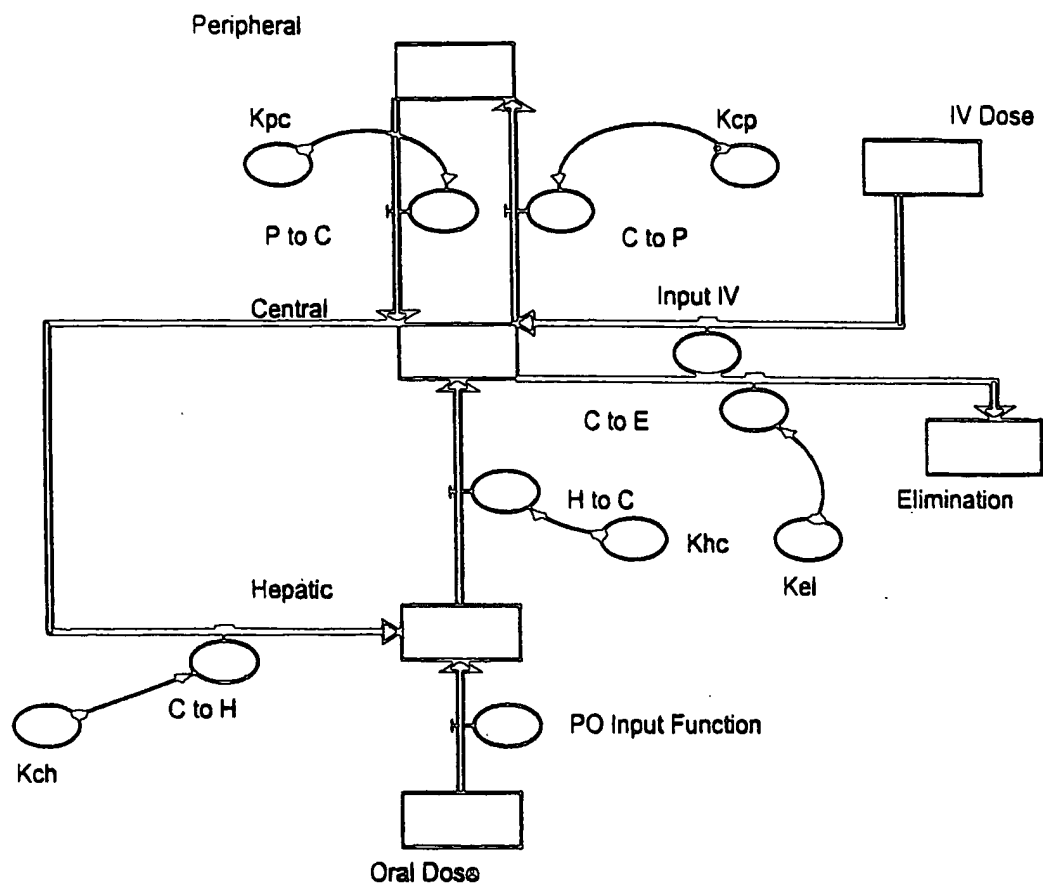


RECEIVED

MAY 05 2003

TECH CENTER 1600/2900

FIG. 19



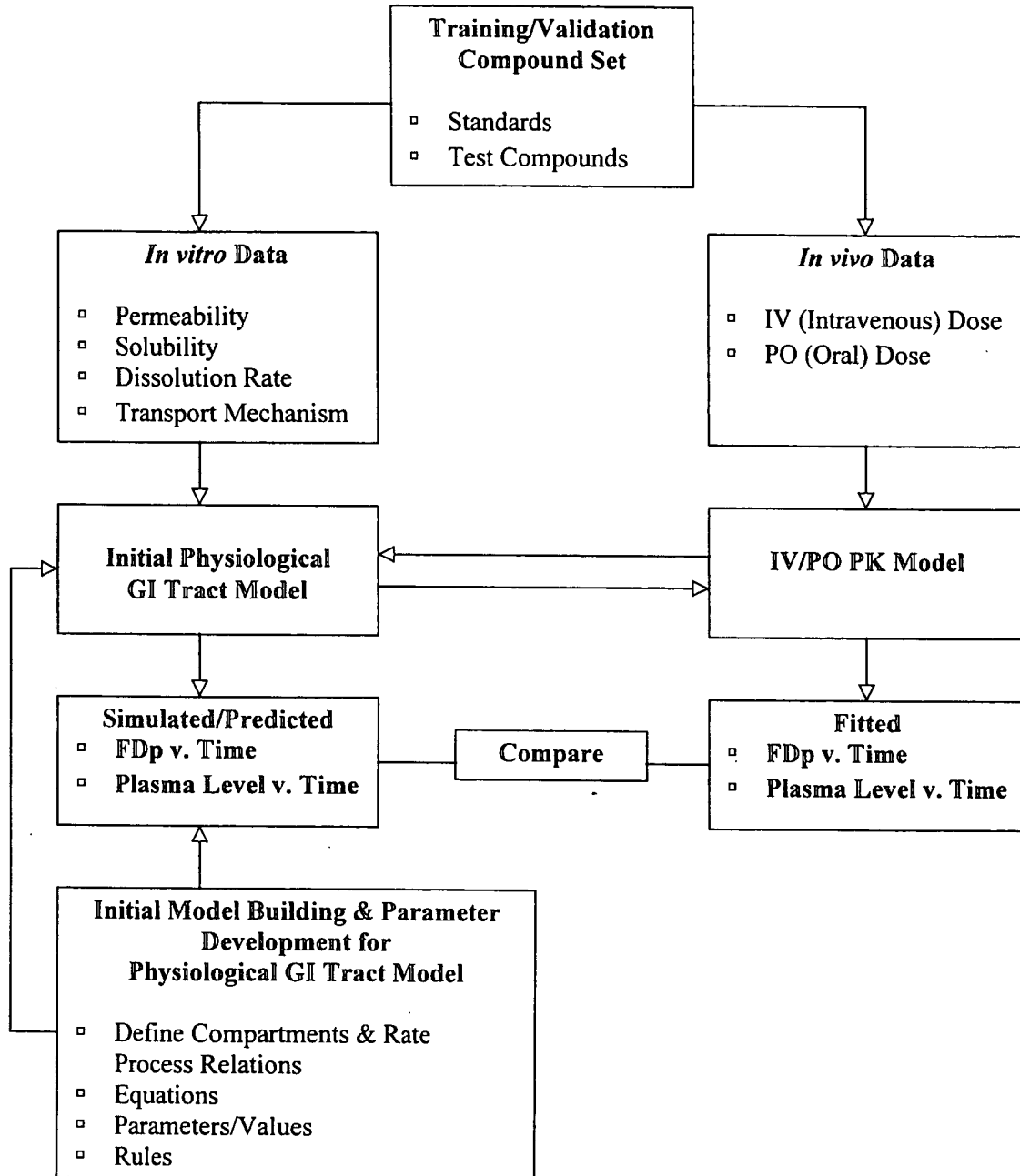


RECEIVED

MAY 05 2003

TECH CENTER 1600/2900

FIG. 20





RECEIVED

MAY 05 2003

TECH CENTER 1600/2900

FIG. 21

Gastrointestinal Transit

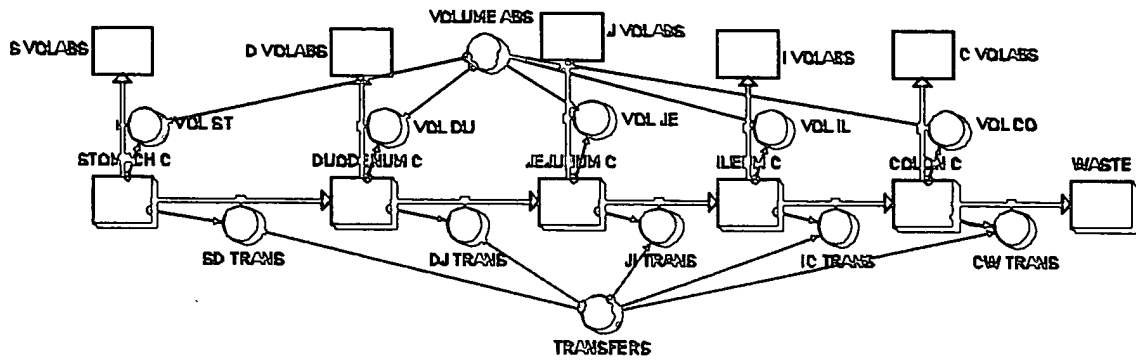
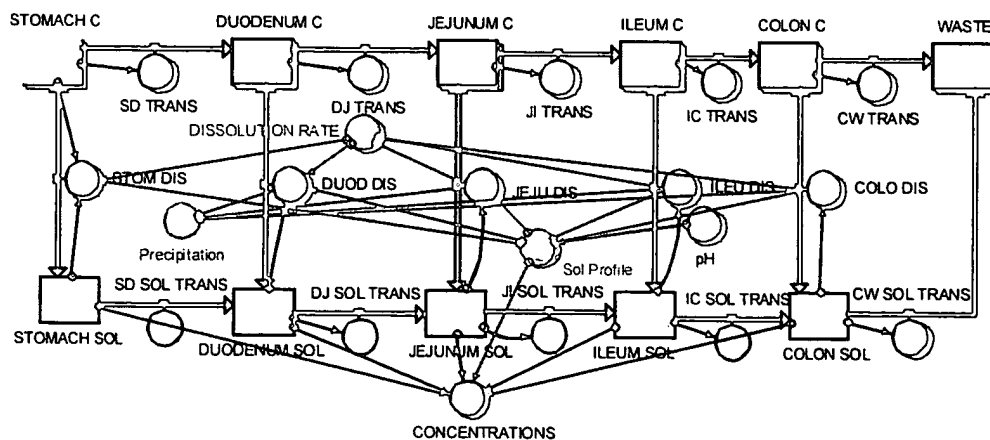


FIG. 22

pH Dependent Solubility and Dissolution





RECEIVED

MAY 05 2003

TECH CENTER 1600/2900

FIG. 23

Absorption

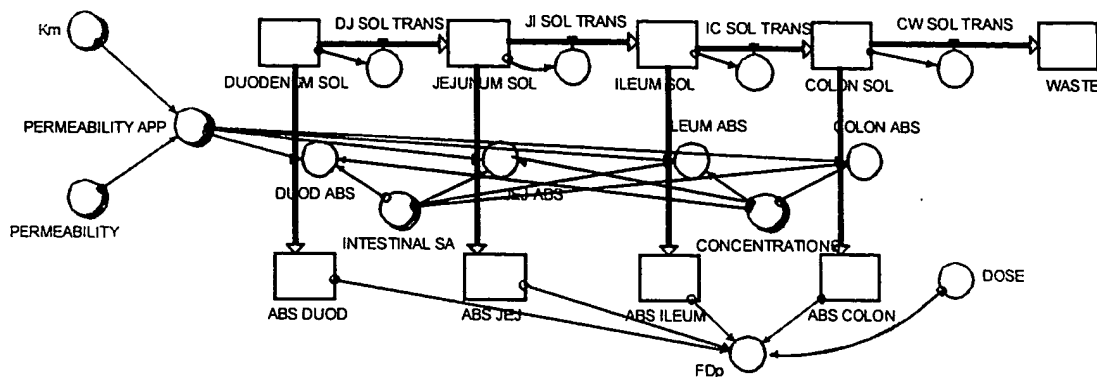
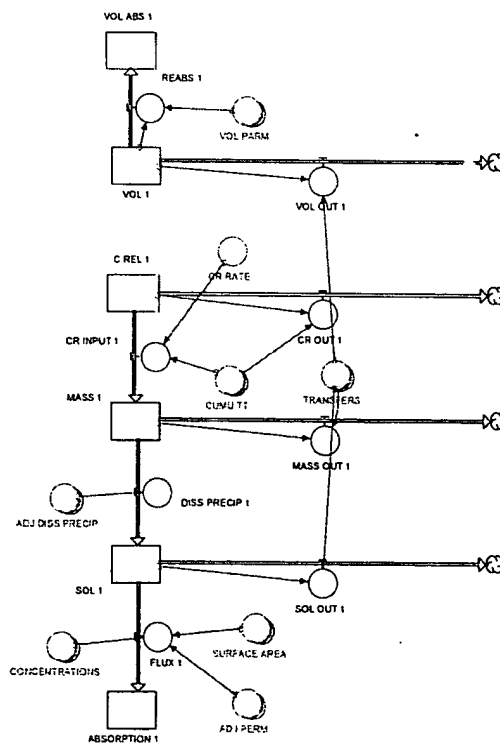


FIG. 24

GI Tract-Intestinal Model





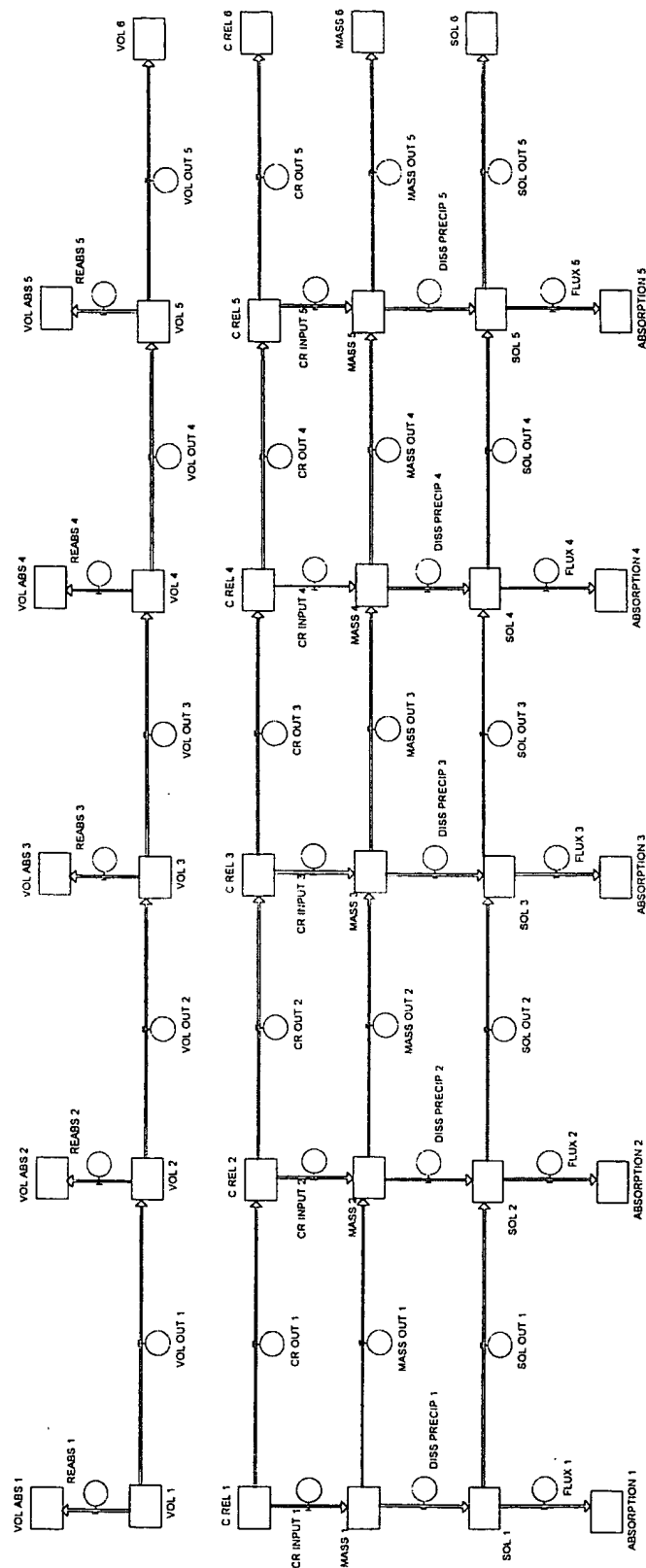
RECEIVED

MAY 05 2003

TECH CENTER 1600/2900

FIG. 25

GI Tract-Intestinal Model (without converters, ghosts or connectors)





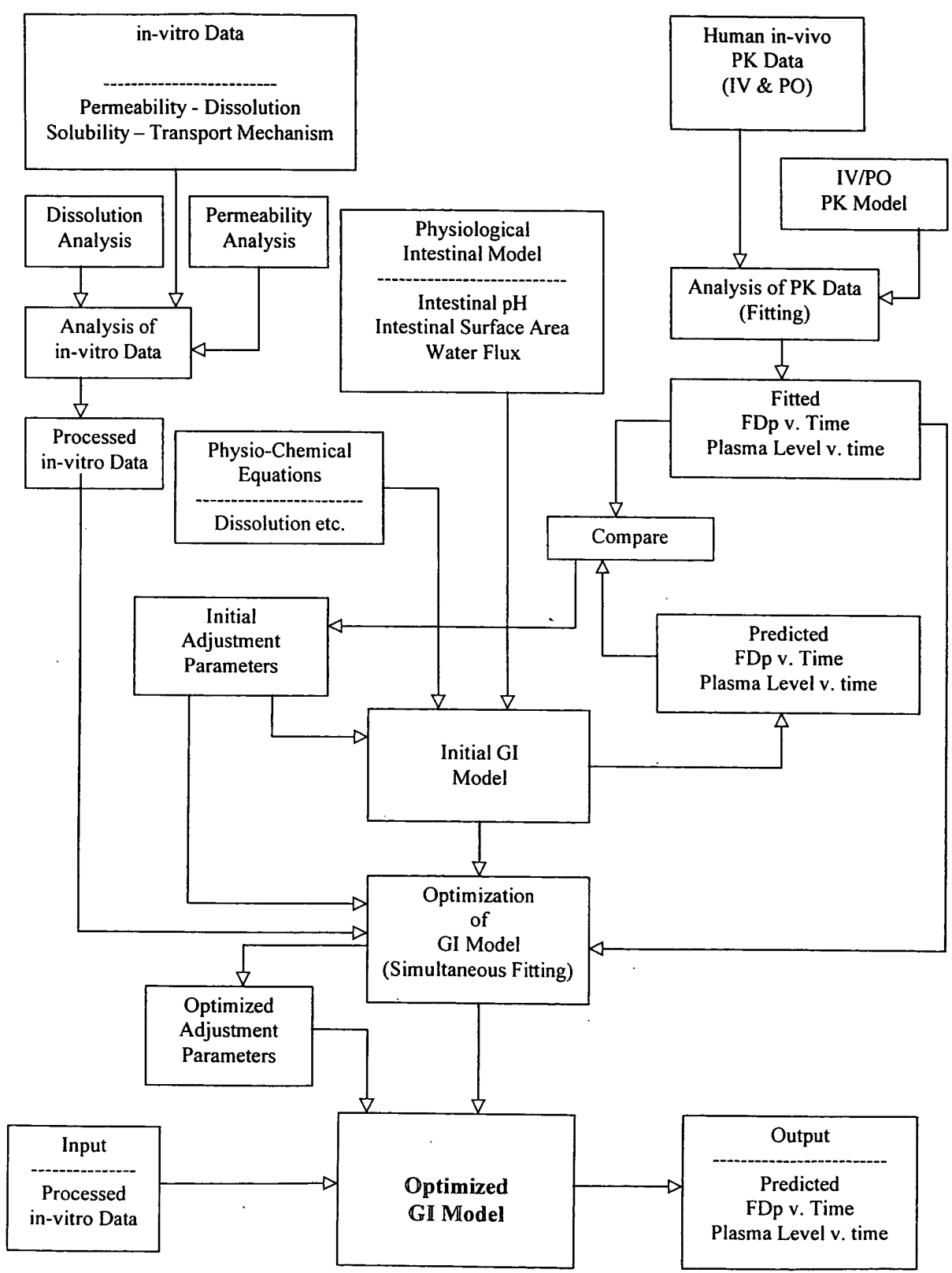


RECEIVED

MAY 05 2003

TECH CENTER 1600/2900

FIG. 27





RECEIVED

MAY 05 2003

TECH CENTER 1600/2900

FIG. 28

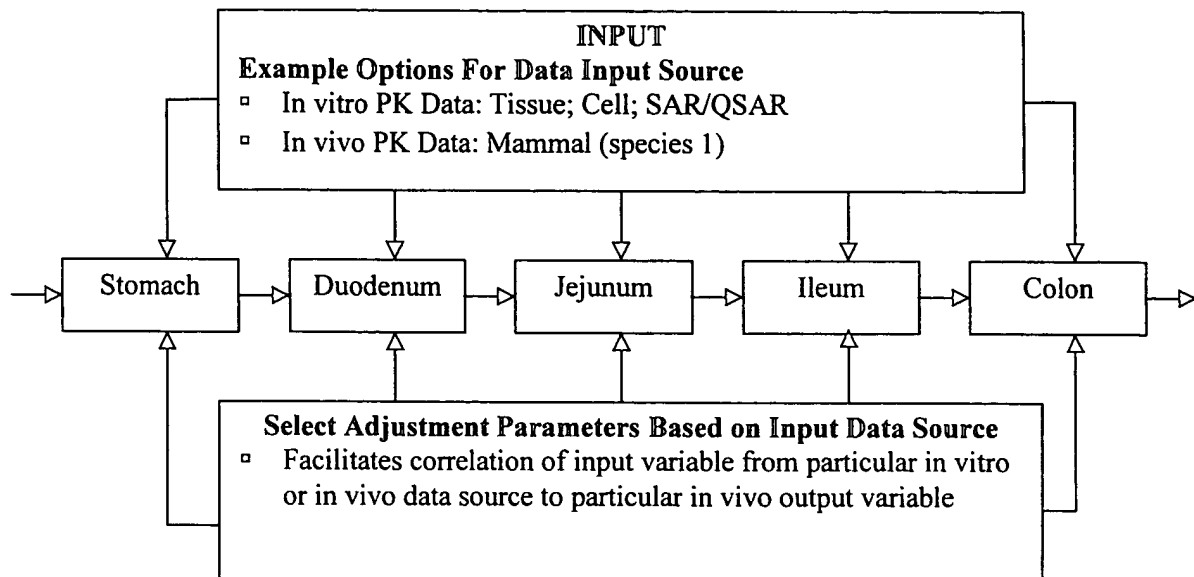
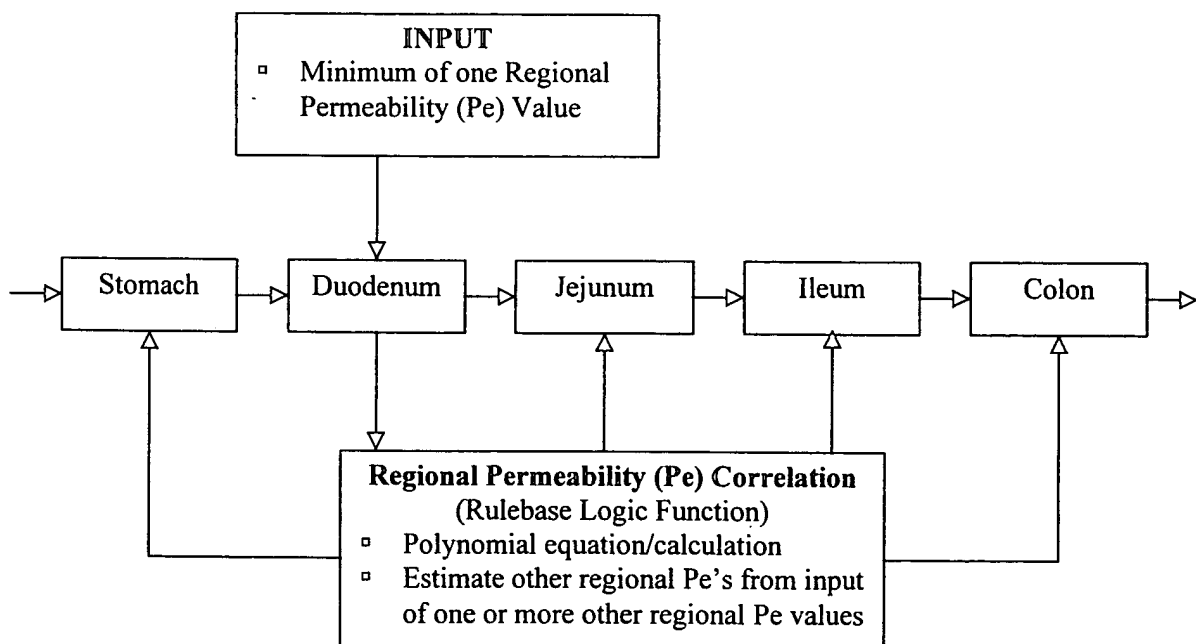


FIG. 29





RECEIVED

MAY 05 2003

TECH CENTER 1600/2900

FIG. 30

Parameters

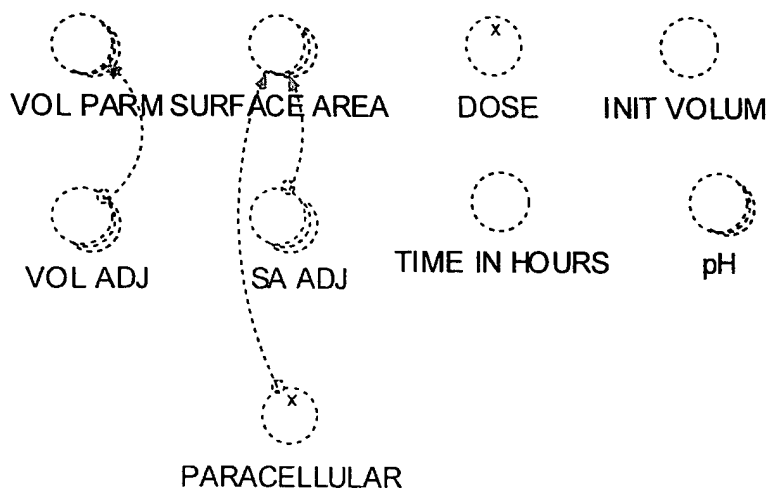
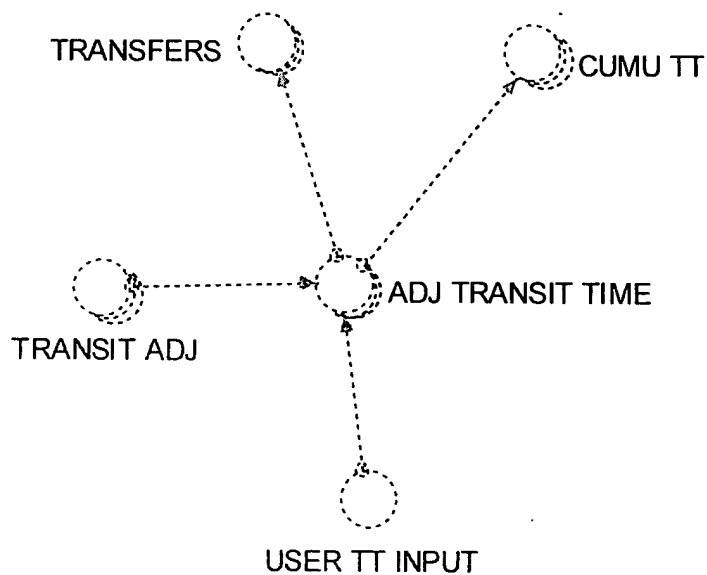


FIG. 31

Transit Time





RECEIVED

MAY 05 2003

TECH CENTER 1600/2900

FIG. 32

Permeability Calculation

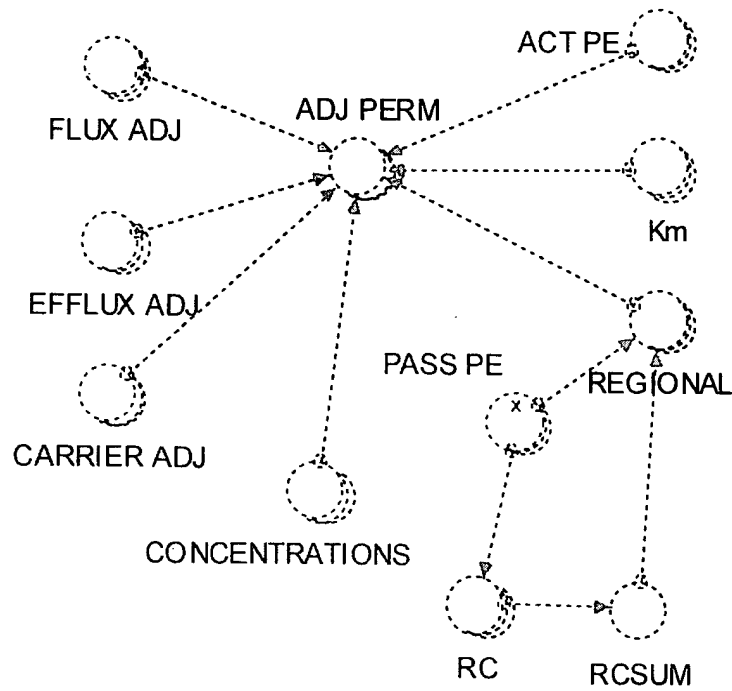
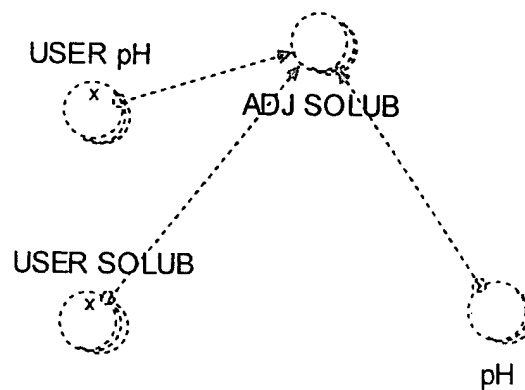


FIG. 33

Solubility Calculation





RECEIVED

MAY 05 2003

TECH CENTER 1600/2900

FIG. 34

Control Release Calculation

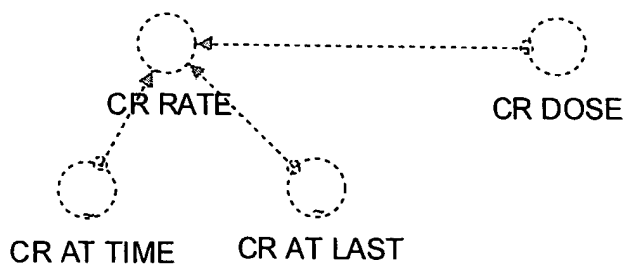
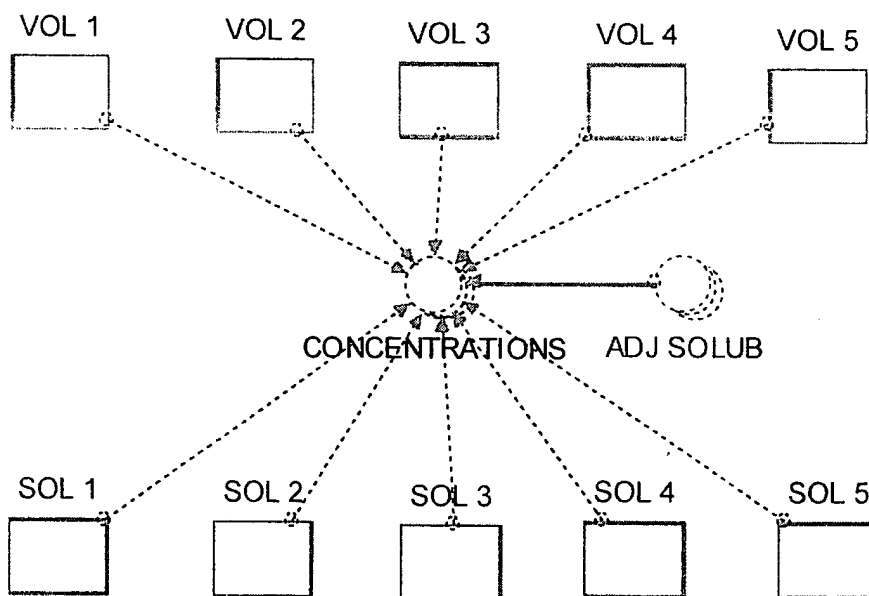


FIG. 35

Concentration Calculation





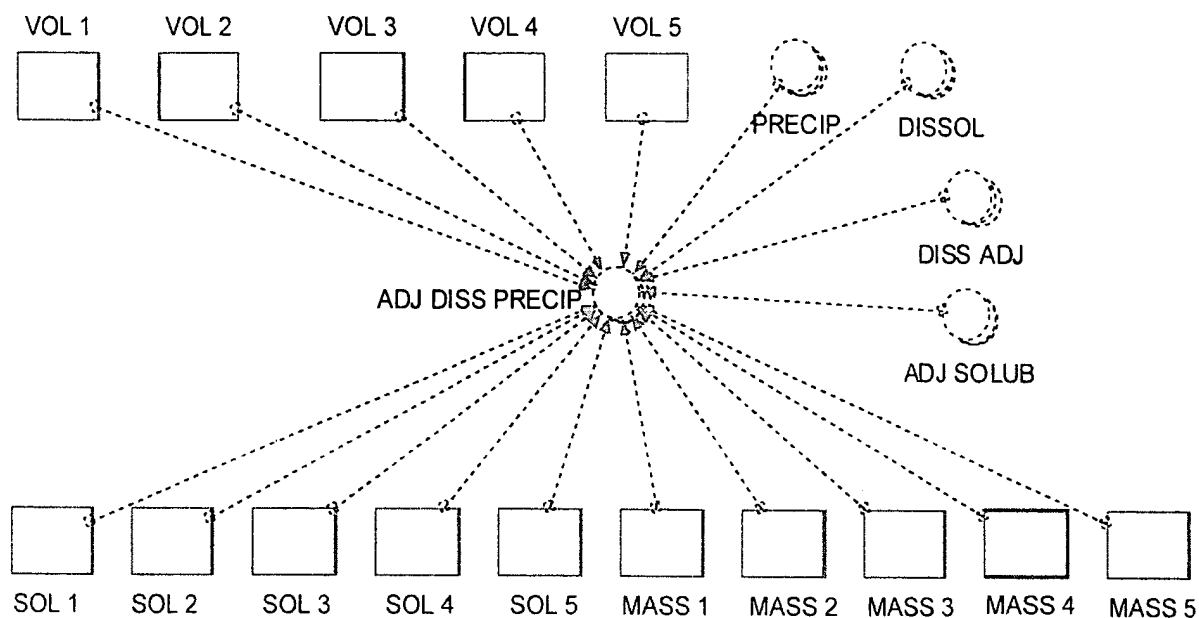
RECEIVED

MAY 05 2003

TECH CENTER 1600/2900

FIG. 36

Dissolution Calculation





RECEIVED

MAY 05 2003

TECH CENTER 1600/2900

FIG. 37

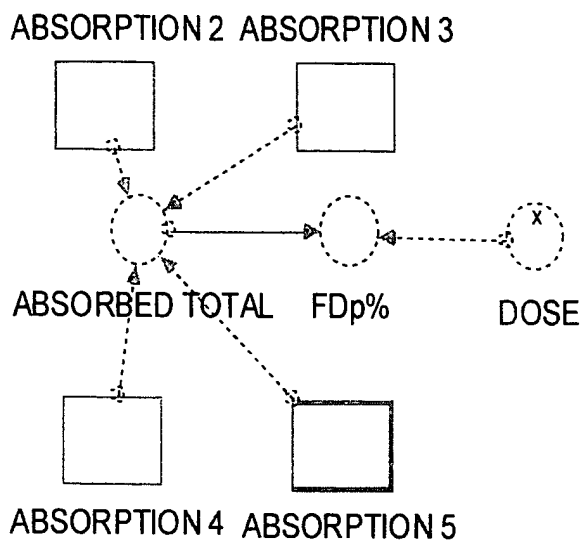
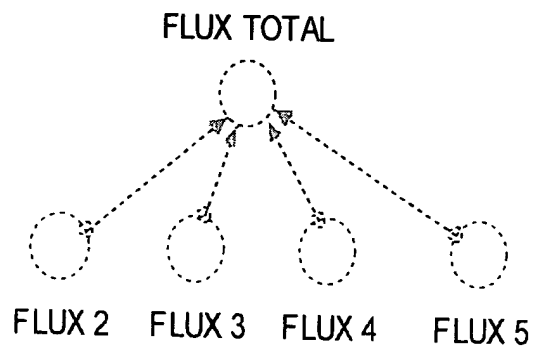


FIG. 38





RECEIVED

MAY 05 2003

TECH CENTER 1600/2900

FIG. 39

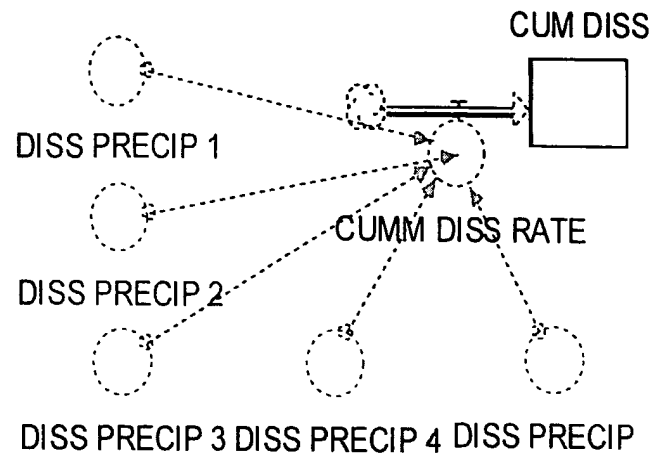
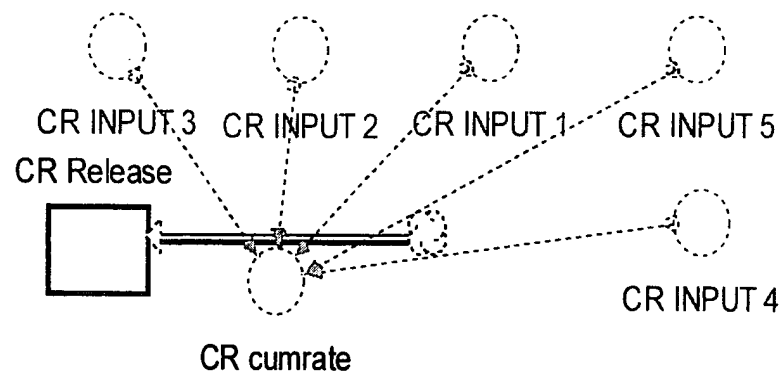


FIG. 40





RECEIVED

MAY 05 2003

FIG. 41

TECH CENTER 1600/2900

Physiological GI Tract Model

Database

- **GI Segment Compartments**
 - Fluid Absorption
 - Fluid Volume
 - Insoluble Mass
 - Soluble Mass
 - Soluble Mass Absorption
 - Dosage Form Mass
- **GI Segment Flow Regulators**
 - Fluid Absorption Rate
 - Fluid Volume Transit Rate
 - Insoluble Mass Transit Rate
 - Insoluble Mass Dissolution Rate
 - Soluble Mass Transit Rate
 - Soluble Mass Absorption Rate
 - Dosage Form Disintegration/Release Rate
- **GI Segment Converters**
 - Fluid Volume Absorption Rate Constant
 - GI Transit Rate Constant
 - Adjusted Dissolution Rate Constant
 - Dissolved Drug Concentration
 - Adjusted Surface Area
 - Adjusted Permeability

Rulebase

- GI Transit
- Dissolution
- Absorption
- Permeability Calculations
- Concentration Calculations
- Computational Error Corrections



RECEIVED

MAY 05 2003

TECH CENTER 1600/2900

FIG. 42

Physiological GI Tract Model

- **GI Segment Compartments & Flow Regulators**
 - **Fluid Absorption**
 - *Fluid Absorption Rate*
 - **Fluid Volume**
 - *Fluid Volume Absorption Rate*
 - *Fluid Volume Transit Rate*
 - **Insoluble Mass**
 - *Insoluble Mass Transit Rate*
 - *Insoluble Mass Dissolution Rate*
 - **Soluble Mass**
 - *Insoluble Mass Dissolution Rate*
 - *Soluble Mass Transit Rate*
 - *Soluble Mass Absorption Rate*
 - **Soluble Mass Absorption**
 - *Soluble Mass Absorption Rate*

FIG. 43

Physiological GI Tract Model

- **GI Segments Flow Regulators & Converters**
 - **Fluid Absorption Rate**
 - *Fluid Volume*
 - *Fluid Volume Absorption Rate Constant*
 - **Fluid Volume Transit Rate**
 - *Fluid Volume*
 - *Fluid Volume Transit Rate Constant*
 - **Insoluble Mass Transit Rate**
 - *Insoluble Mass*
 - *Insoluble Mass Transit Rate Constant*
 - **Insoluble Mass Dissolution Rate**
 - *Insoluble Mass*
 - *Dissolution Rate Constant*
 - **Soluble Mass Transit Rate**
 - *Soluble Mass*
 - *Soluble Mass Transit Rate Constant*
 - **Soluble Mass Absorption Rate (Flux)**
 - *Surface Area*
 - *Dissolved Mass Concentration*
 - *Permeability*



RECEIVED

MAY 05 2003

TECH CENTER 1600/2900

FIG. 44

Physiological GI Tract Model

- **Converters**
 - **Permeability**
 - Passive Absorption Adjustment Parameter
 - Efflux/Secretion Adjustment Parameter
 - Active Absorption Adjustment Parameter
 - Active or Carrier Mediated Absorptive Permeability
 - Km
 - Passive Permeability/Regional Correlation
 - Passive Permeability
 - Logic Function For Regional Correlation
 - Passive Permeability
 - Logic Function For Regional Correlation
 - Dissolved Mass Concentrations
 - **Dissolved Mass Concentration**
 - Fluid Volume
 - Solubility
 - pH
 - Solubility
 - **Dissolution Rate Constant**
 - Fluid Volume
 - Precipitation Rate Constant
 - Dissolution Rate Adjustment Parameter
 - Solubility
 - Insoluble Mass
 - Soluble Mass
 - **Surface Area**
 - Surface Area Adjustment Parameter
 - Transport Mechanism
 - **Transit Rate**
 - Transit Time Adjustment Parameter
 - User Adjusted Transit Time
 - **Fluid Volume Absorption Rate Constant**
 - Fluid Volume Adjustment Parameter



RECEIVED

MAY 05 2003

TECH CENTER 1600/2900

FIG. 45

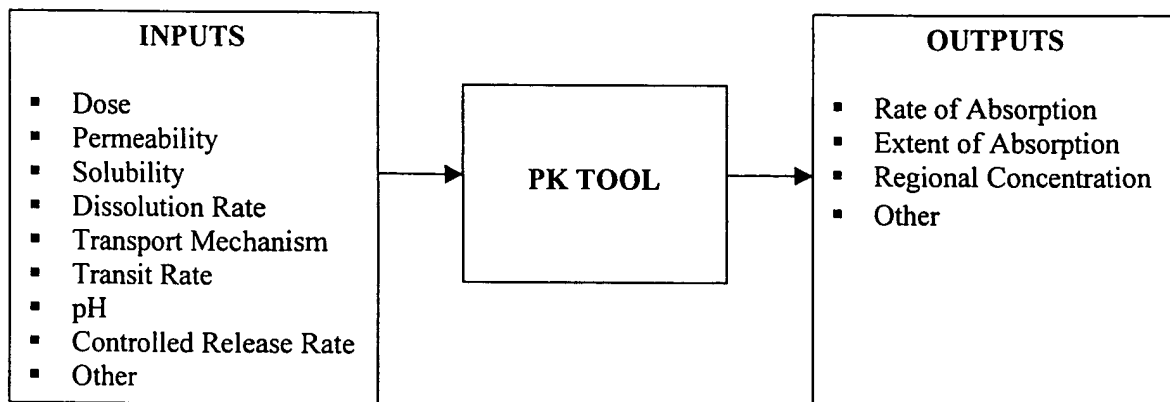
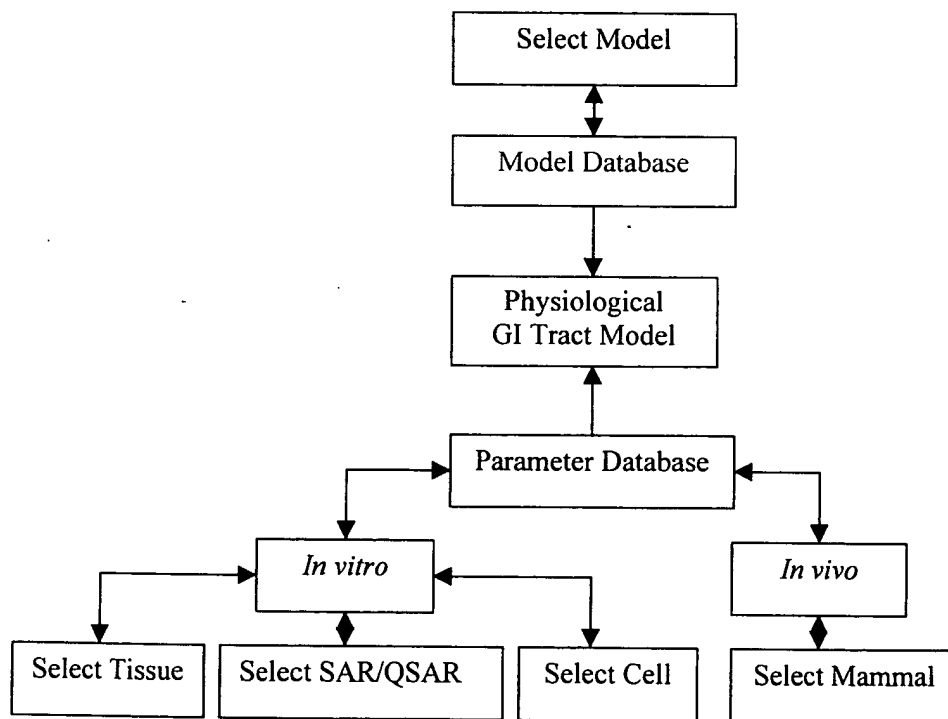


FIG. 46



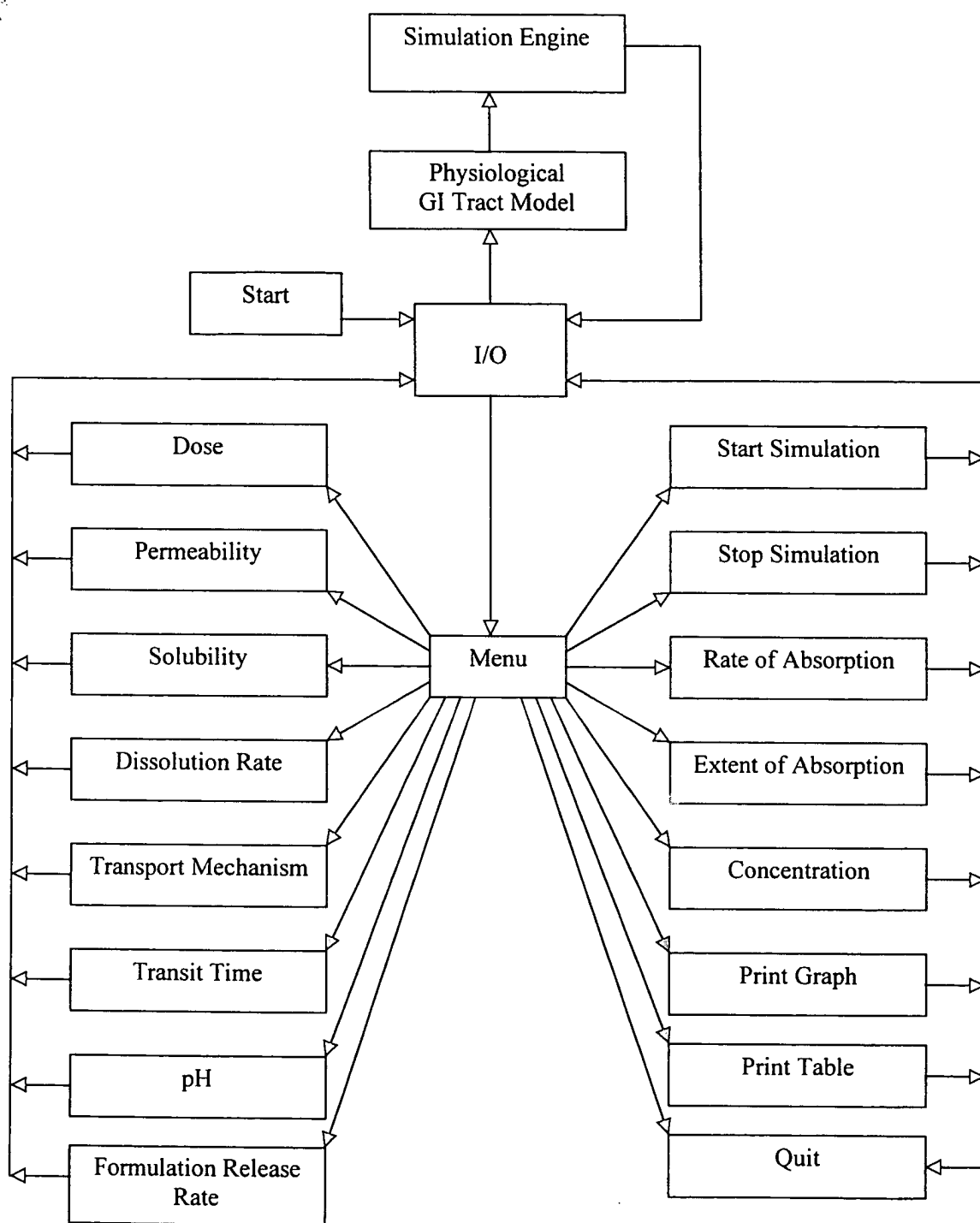


RECEIVED

MAY 05 2003

TECH CENTER 1600/2900

FIG. 47



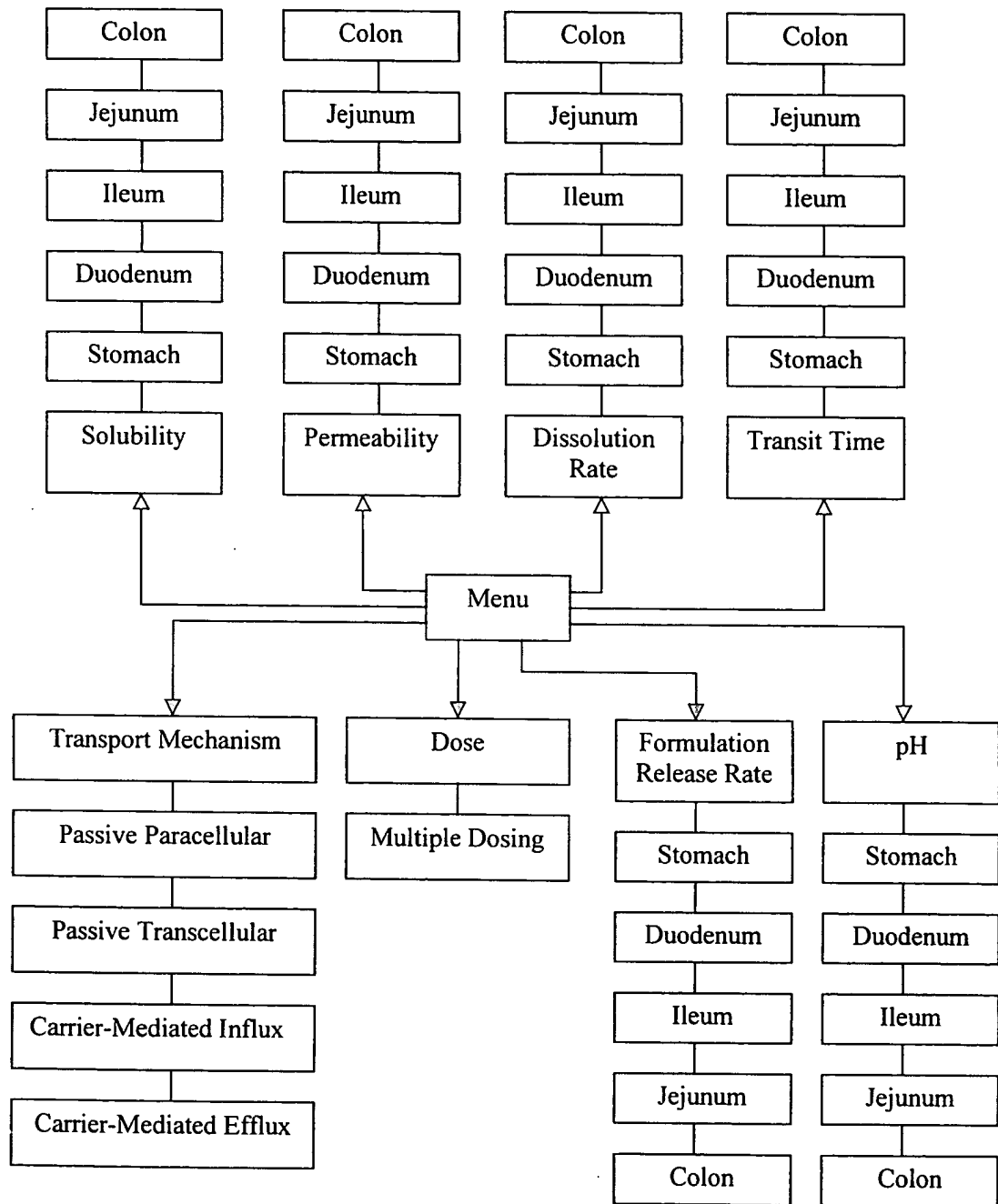


RECEIVED

MAY 05 2003

TECH CENTER 1600/2900

FIG. 48





RECEIVED

MAY 05 2003

TECH CENTER 1600/2900

FIG. 49

Correlation of FDp Extent - GI Model and Pharmacokinetic data

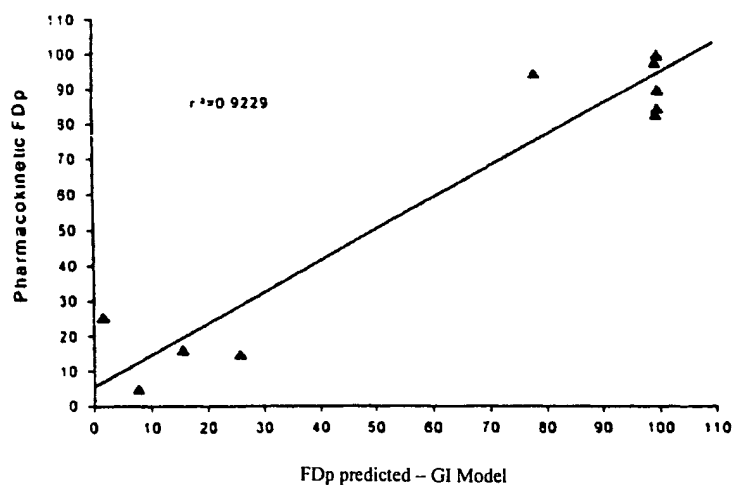
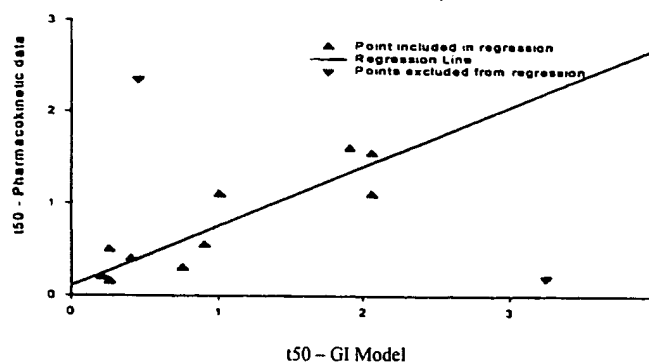


FIG. 50

Correlation of FDp rate of absorption - GI Model and Pharmacokinetic Data





RECEIVED

MAY 05 2003

TECH CENTER 1600/2900

FIG. 51

PO Pharmacokinetic Data
Compound α 1

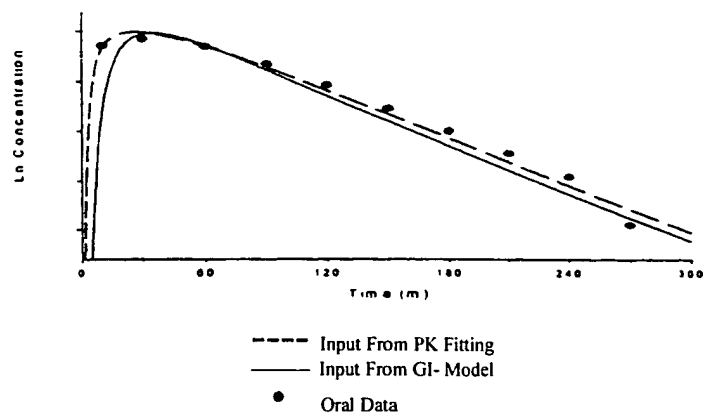
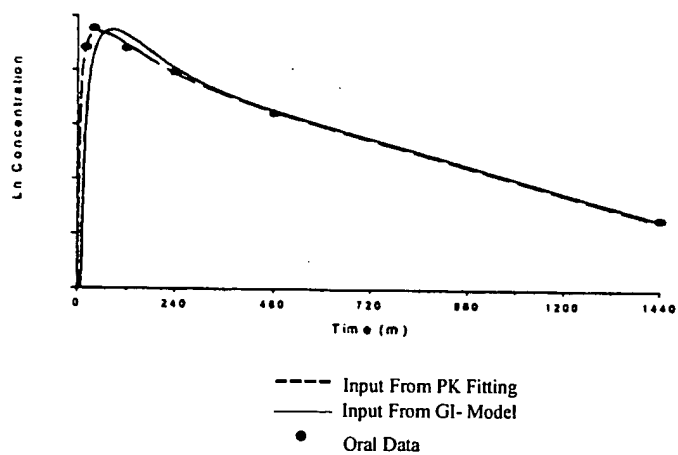


FIG. 52

PO Pharmacokinetic Data
Compound α 4





RECEIVED

MAY 05 2003

TECH CENTER 1600/2900

FIG. 53

PO Pharmacokinetic Data
Compound β 6

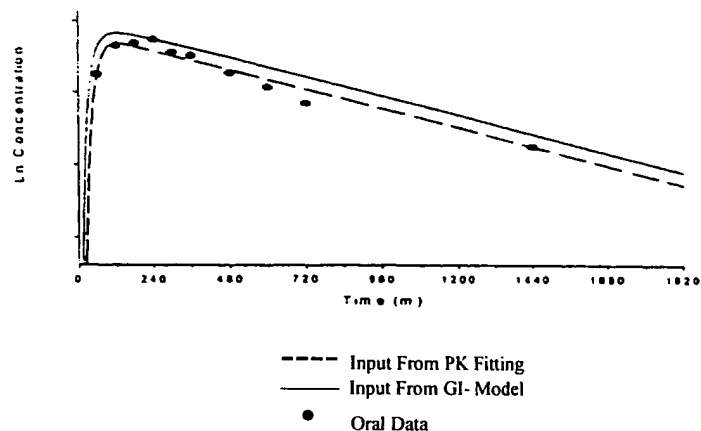




FIG. 54

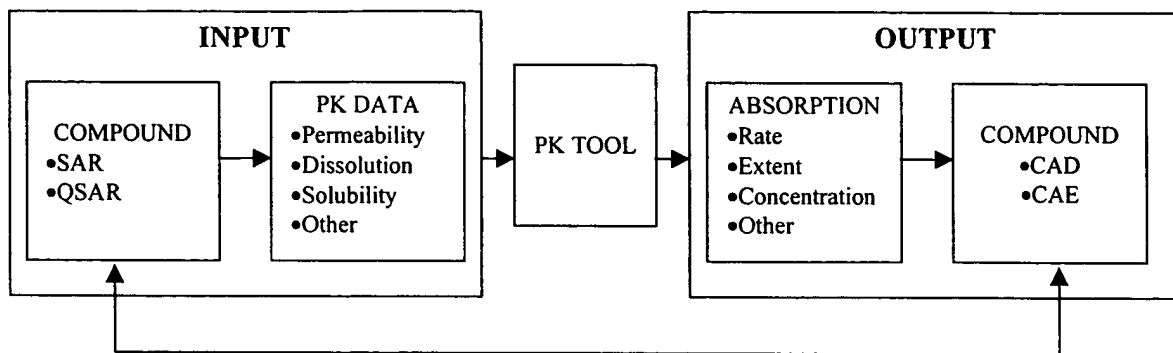
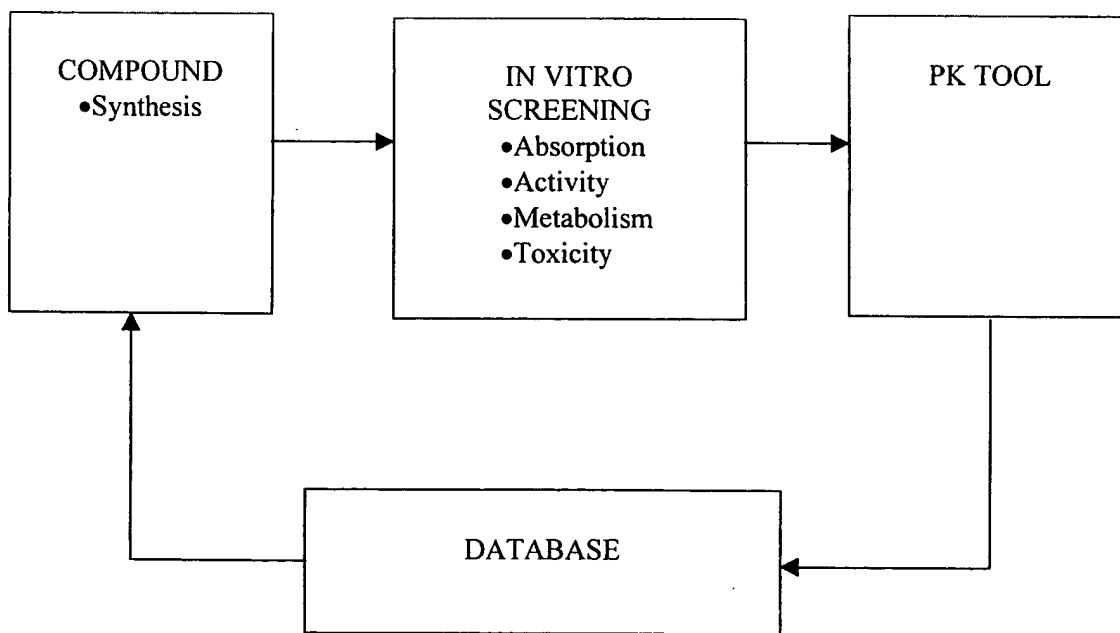
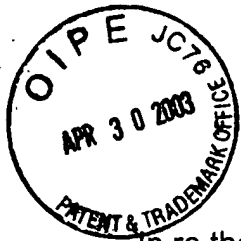


FIG. 55





RECEIVED

MAY 05 2003

TECH CENTER 1600/2900

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the Application of:

Confirmation No.: 6261

GRASS et al.

Art Unit: 1631

Application No.: 09/786,362

Examiner: Ly, Cheyne D.

Filed: June 25, 2001

Attorney Dkt. No.: 109904-00028

For: METHOD FOR SCREENING AND PRODUCING COMPOUND LIBRARIES

SUBMISSION OF FORMAL DRAWINGS

Commissioner for Patents
Washington, DC 20231


April 30, 2003

Sir:

In response to the Notice of Reply Not Fully Responsive to Prior Office Action dated April 1, 2003 and the Office Action (Restriction Requirement) dated January 31, 2003 attached hereto new formal drawings to replace corresponding sheets containing the informal drawings objected to. It is respectfully submitted that Figs. 1-55 overcome the objections to the originally filed drawings.

If any fees are required with respect to this paper, please charge our Deposit Account No. 01-2300 referring to client-matter number 109904-00028.

Respectfully submitted,



Rustan J. Hill
Registration No. 37,351

1050 Connecticut Avenue, N.W., Suite 400
Washington, D.C. 20036-5339
Tel (202) 857-6000
Fax (202) 638-4810
RJH/sh

Enclosures: Formal Drawings (Figs. 1-55, 36 Sheets)

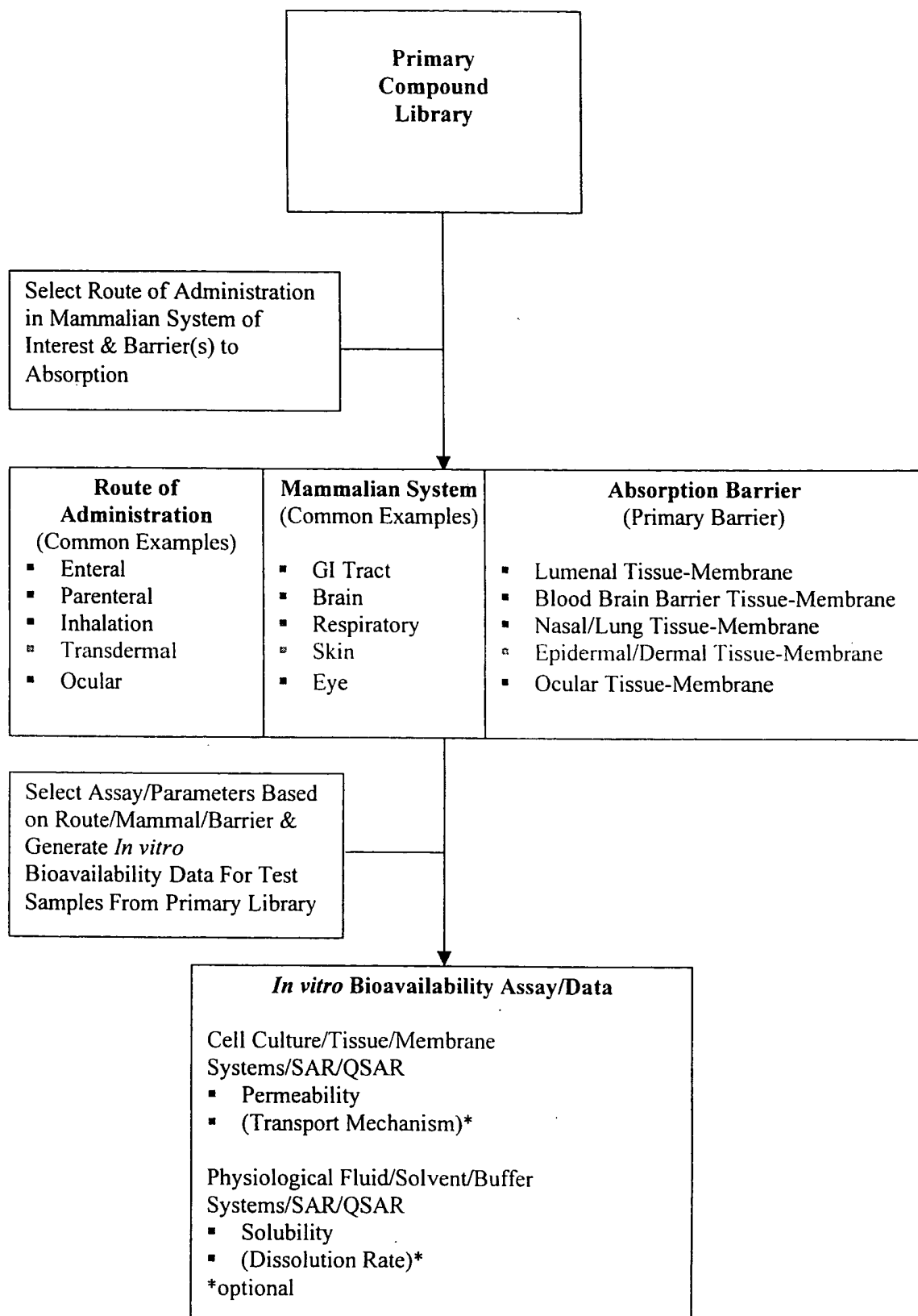


RECEIVED

MAY 05 2003

TECH CENTER 1600/2900

FIG. 1



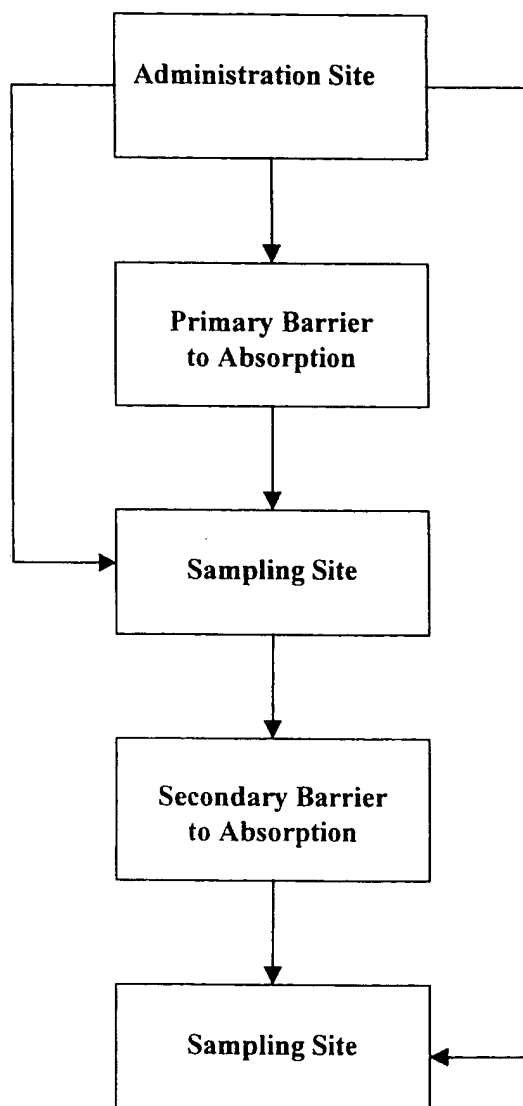


RECEIVED

MAY 05 2003

TECH CENTER 1600/2900

FIG. 2



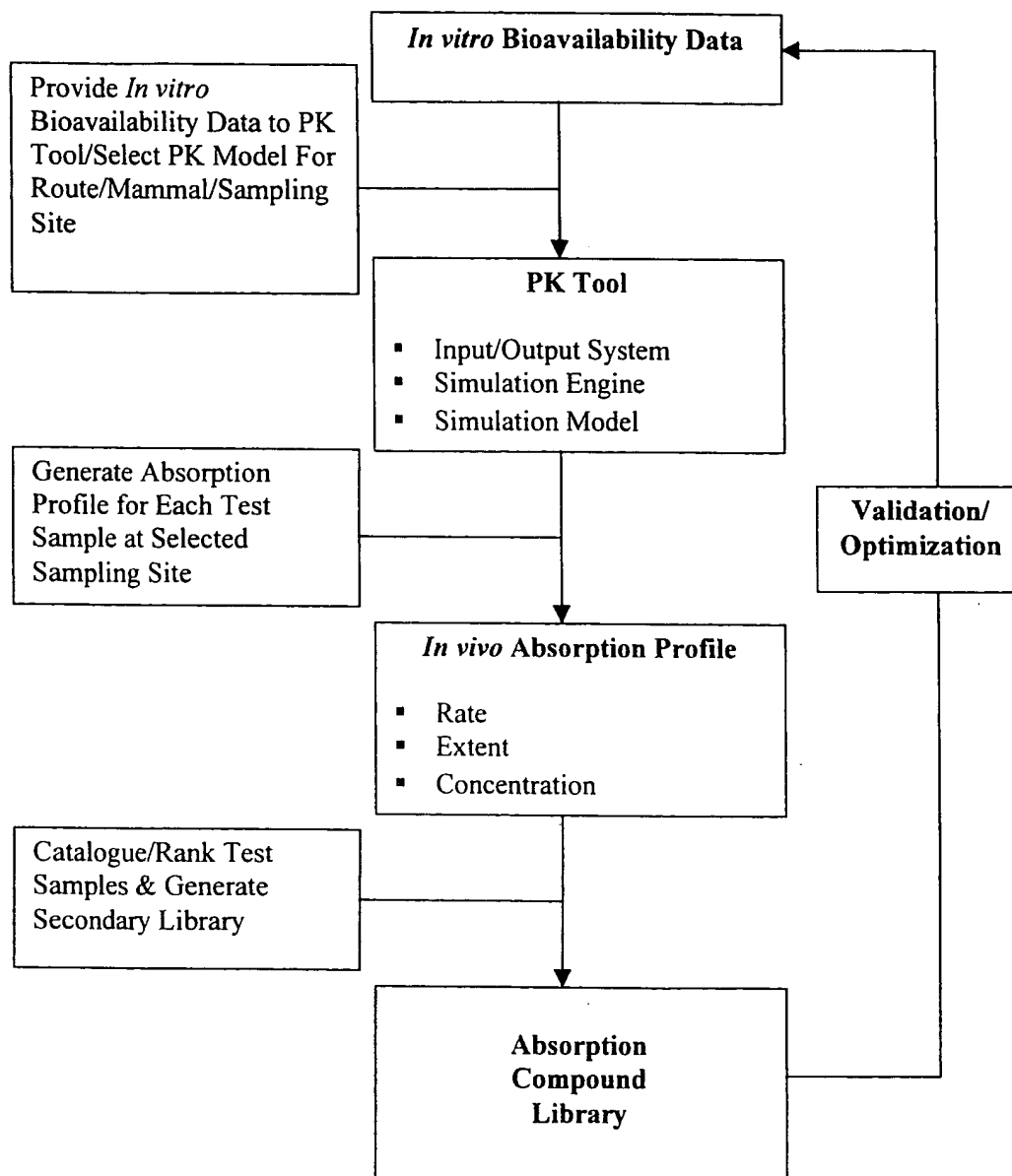


RECEIVED

MAY 05 2003

TECH CENTER 1600/2900

FIG. 3



MAY 05 2003

TECH CENTER 1600/2900

FIG. 4

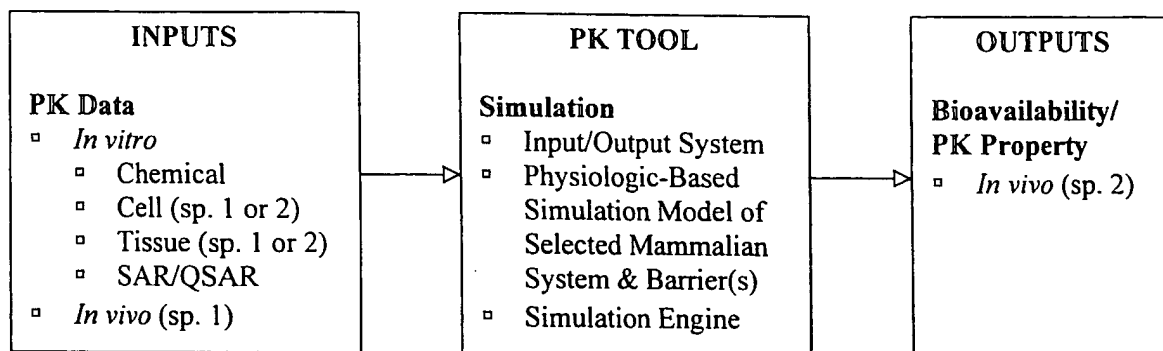
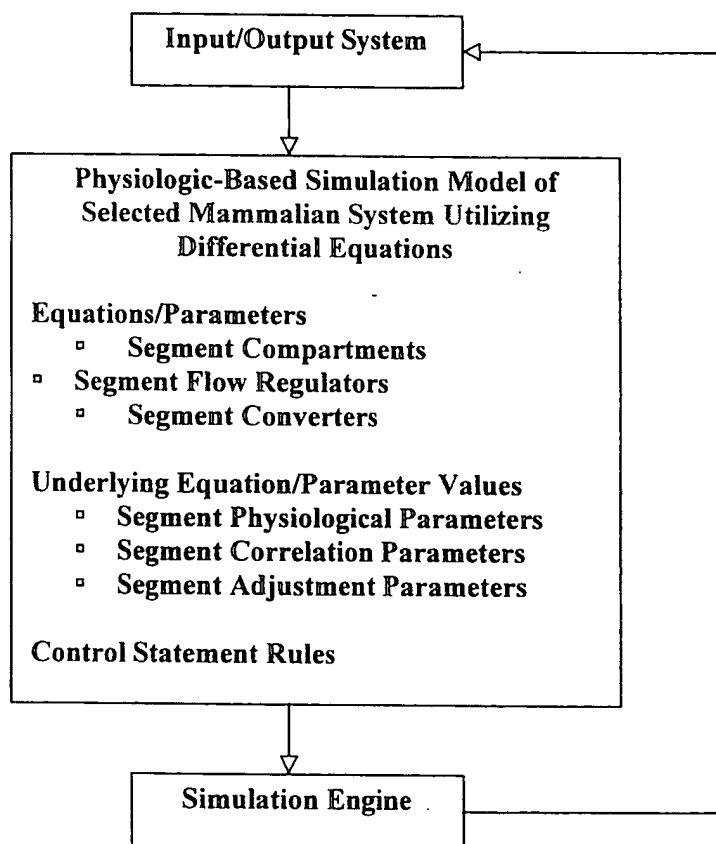


FIG. 5





RECEIVED

MAY 05 2003

TECH CENTER 1600/2900

FIG. 6

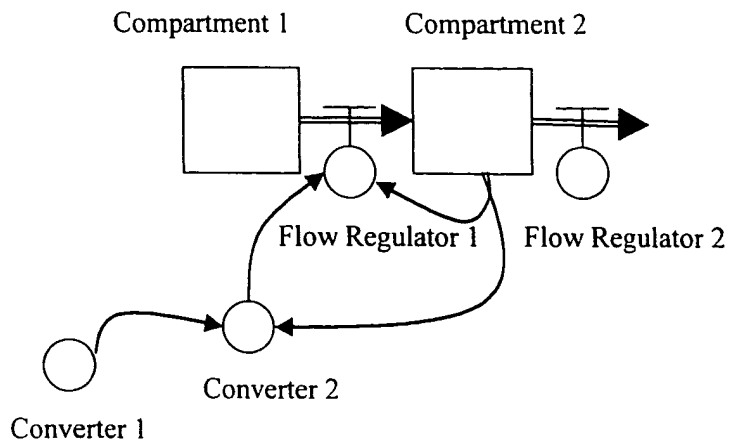


FIG. 7

Symbol	Name	Time-Dependent Function
	Compartment	Equation or value for amount of substance stored.
	Flow Regulator	Rate equation for amount of substance transferred.
	Converter	Equation or pre-defined value for (i) input into flow regulator; (ii) input into another converter; and/or (iii) storing value.
	Input Link	Directs input values.

FIG. 8

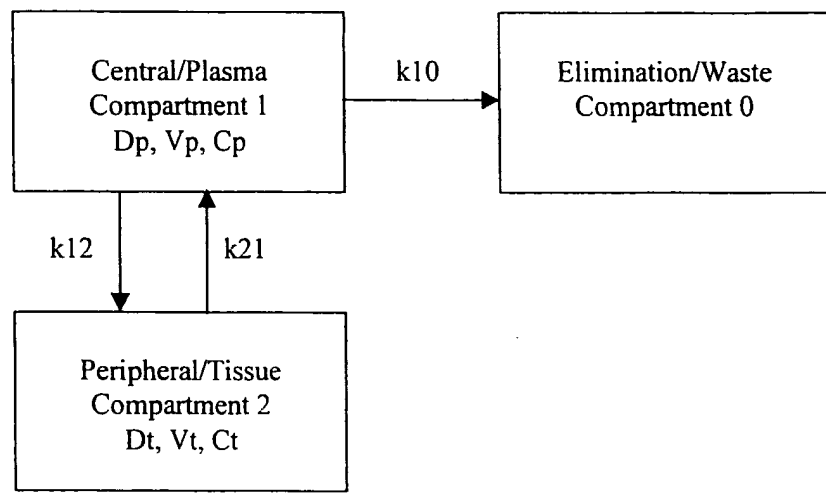
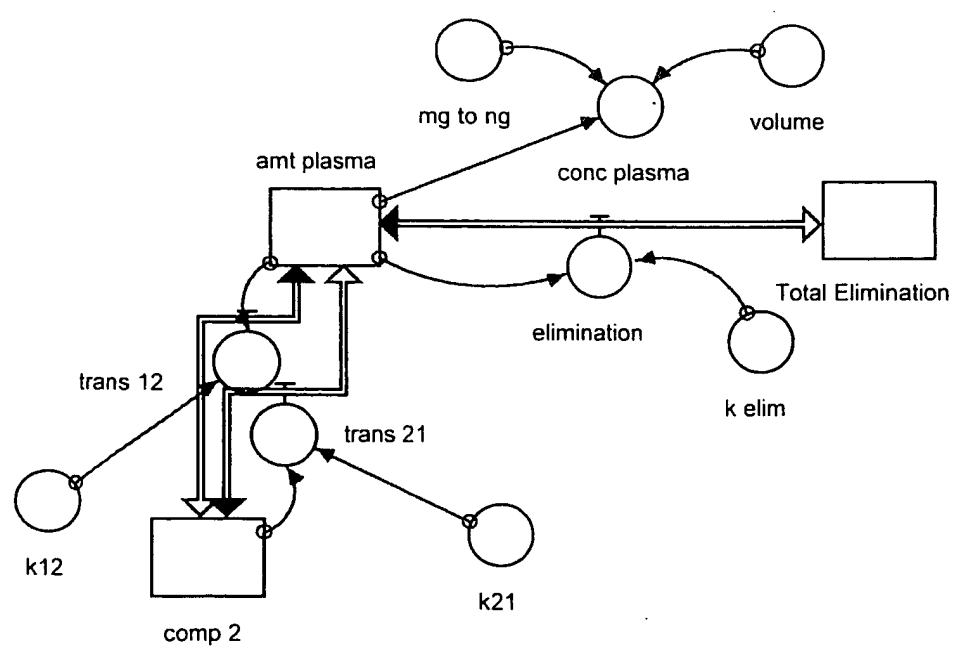


FIG. 9



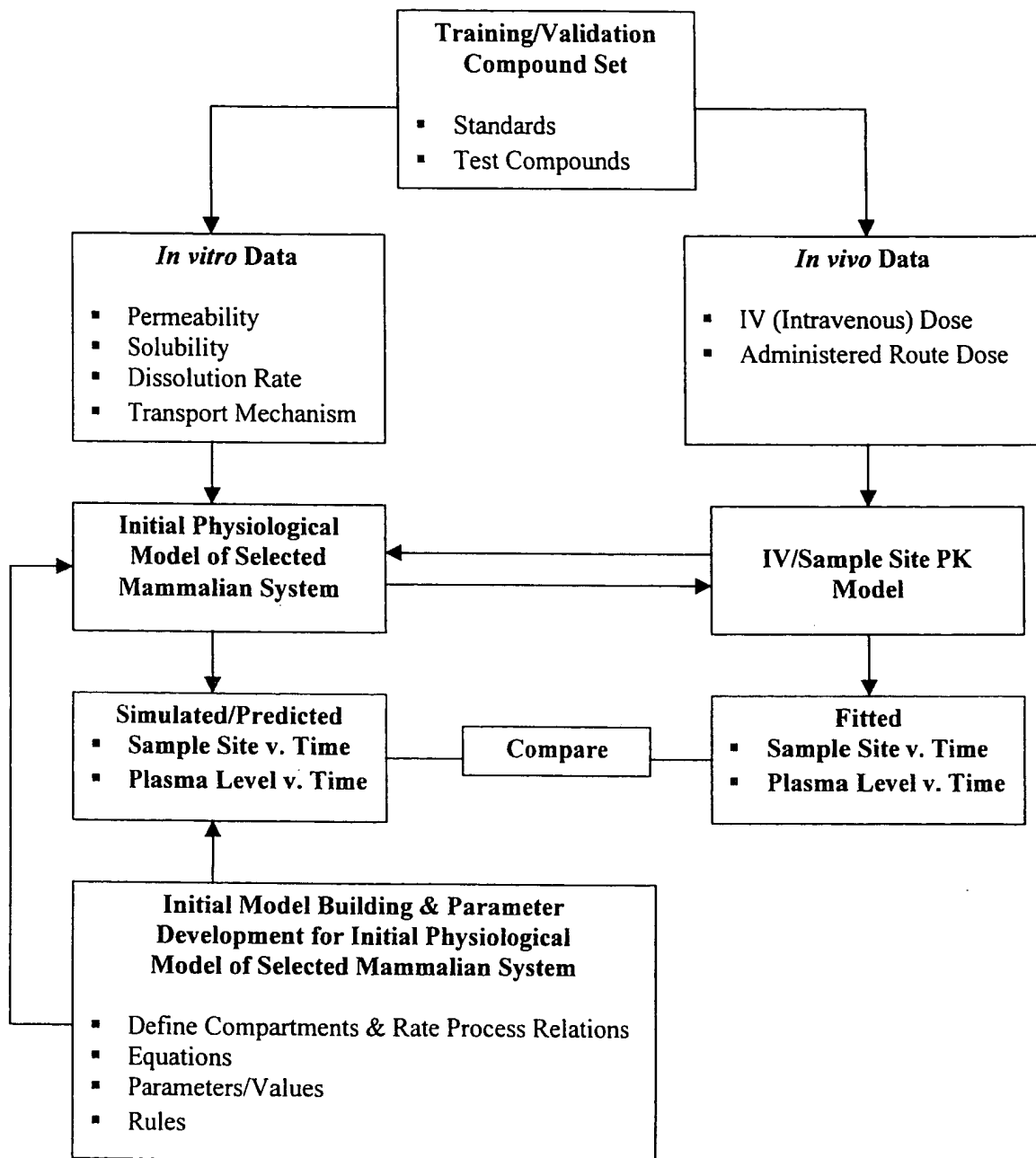


RECEIVED

MAY 05 2003

TECH CENTER 1600/2900

FIG. 10



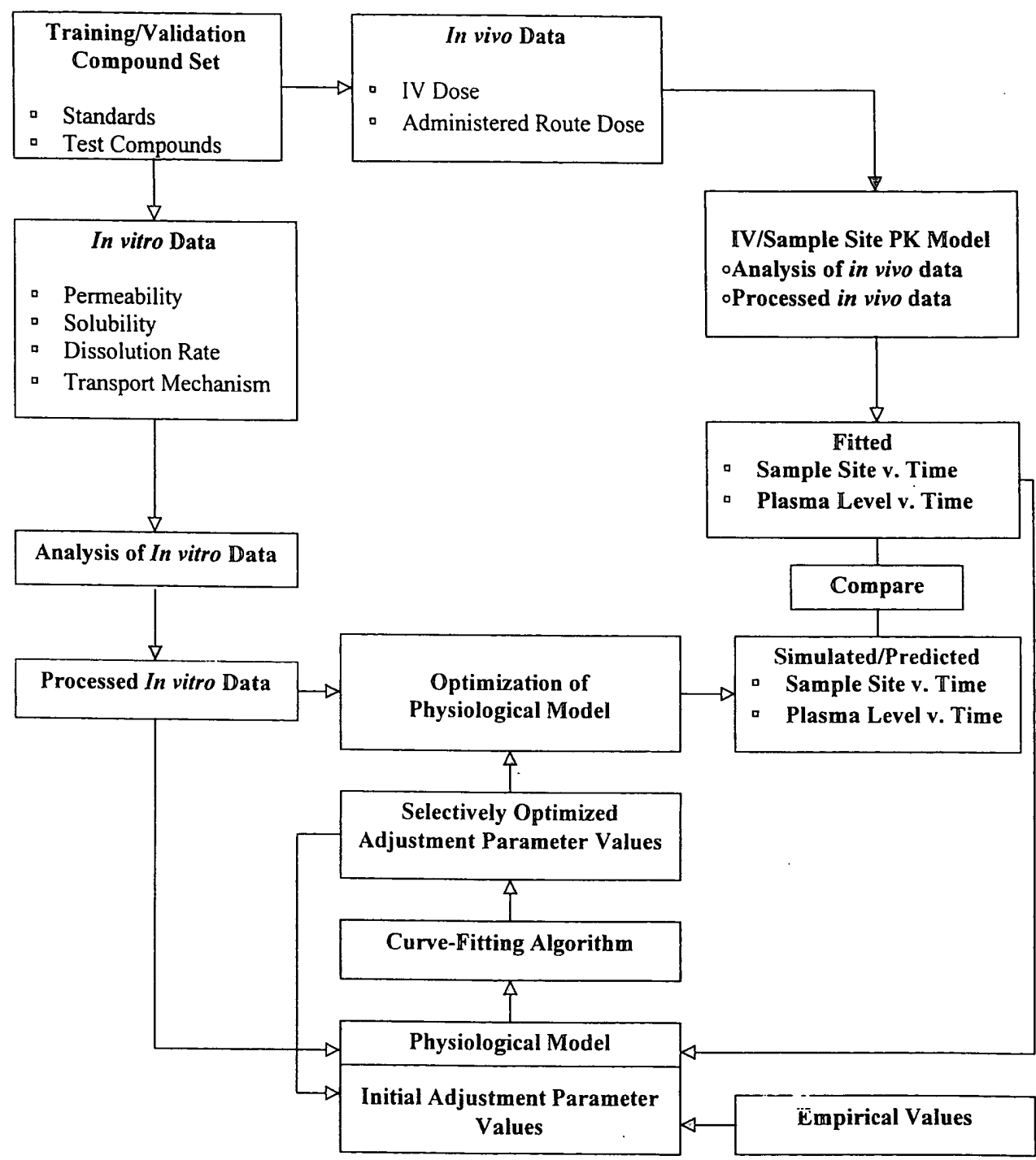


RECEIVED

MAY 05 2003

TECH CENTER 1600/2900

FIG. 11



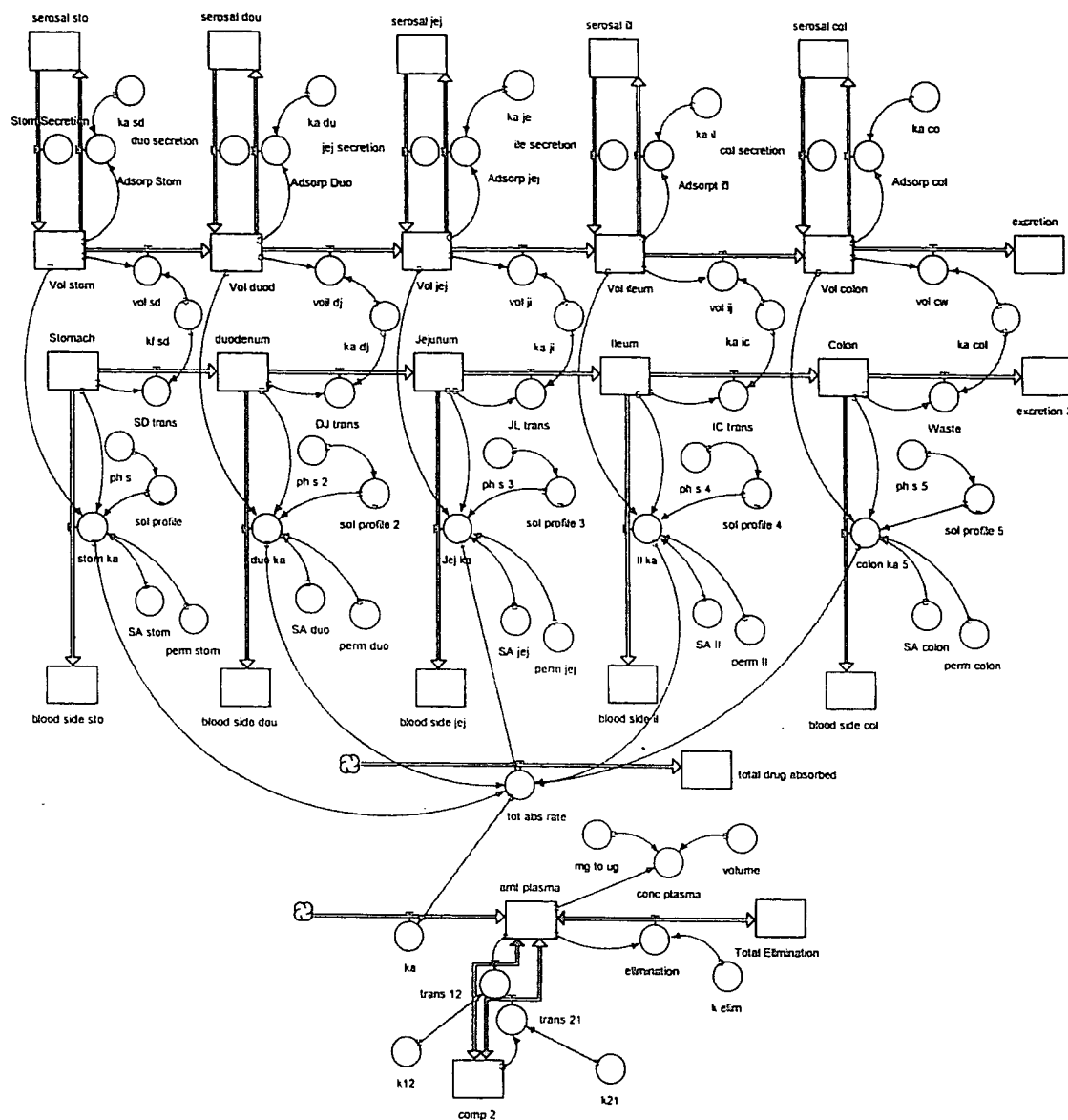


RECEIVED

MAY 05 2003

FIG. 12

TECH CENTER 1600/2900





RECEIVED

MAY 05 2003

TECH CENTER 1600/2900

FIG. 13

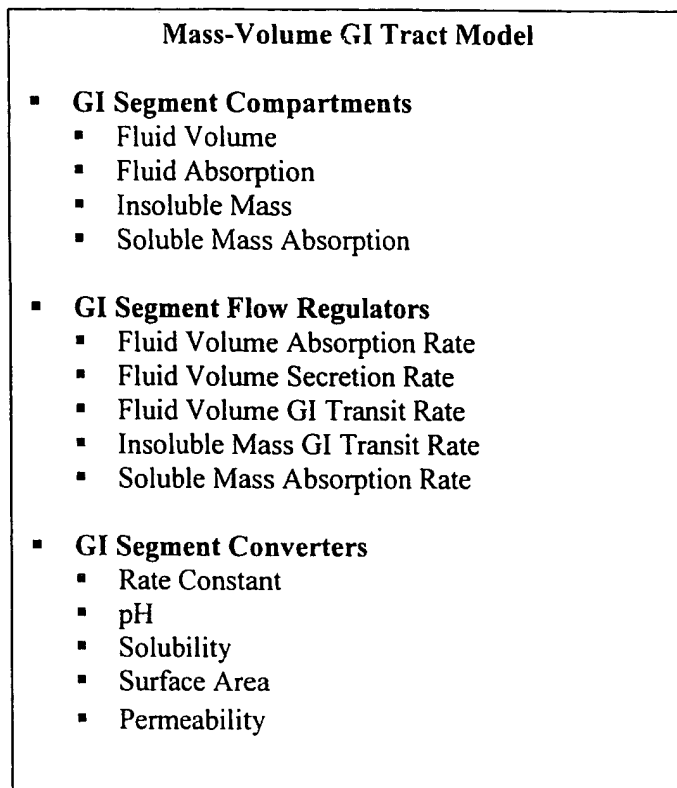
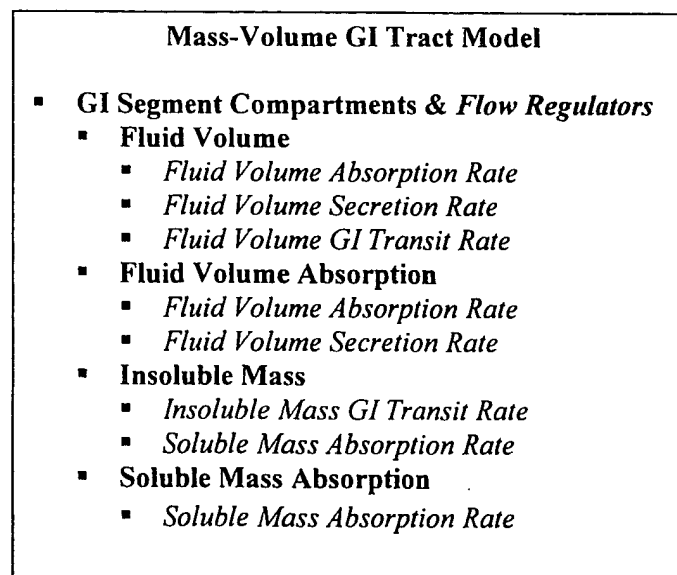


FIG. 14





RECEIVED

MAY 05 2003

TECH CENTER 1600/2900

FIG. 15

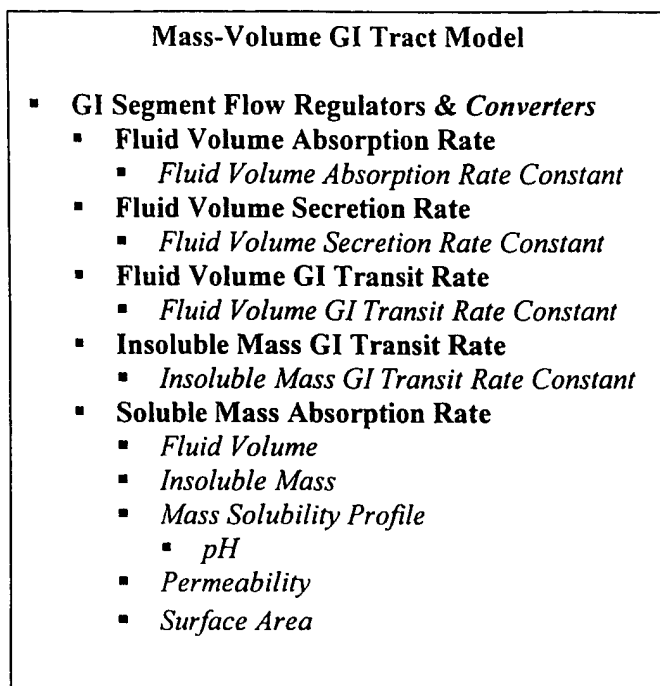
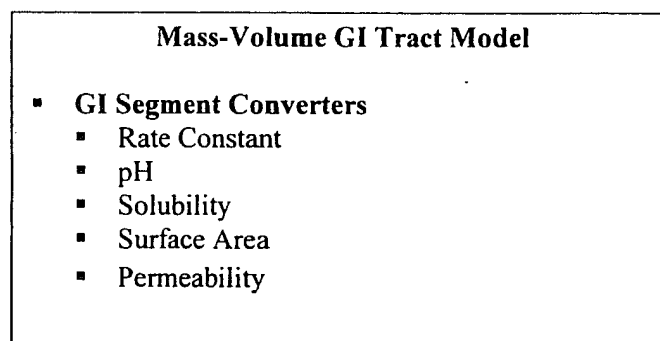


FIG. 16





RECEIVED

MAY 05 2003

TECH CENTER 1600/2900

FIG. 17

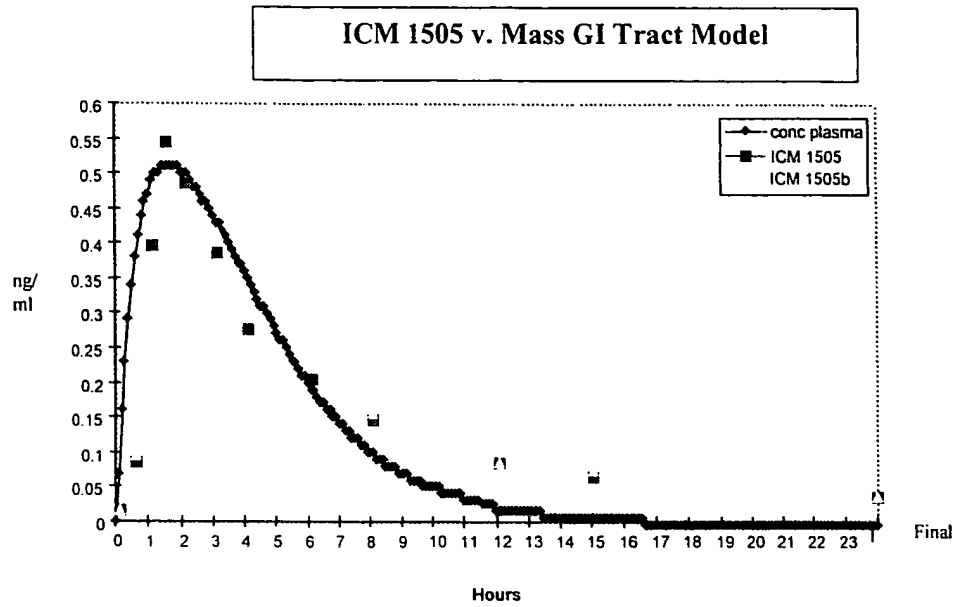


FIG. 18

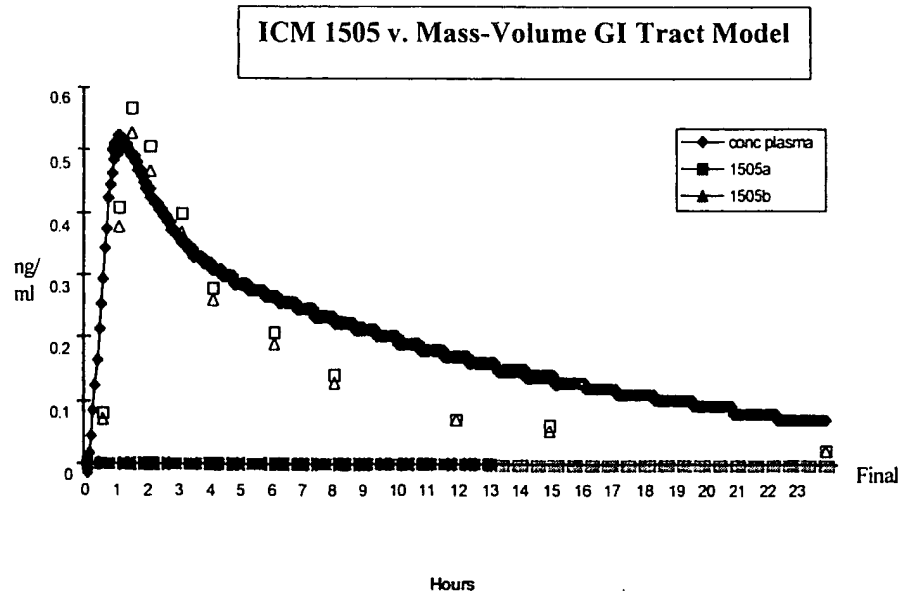


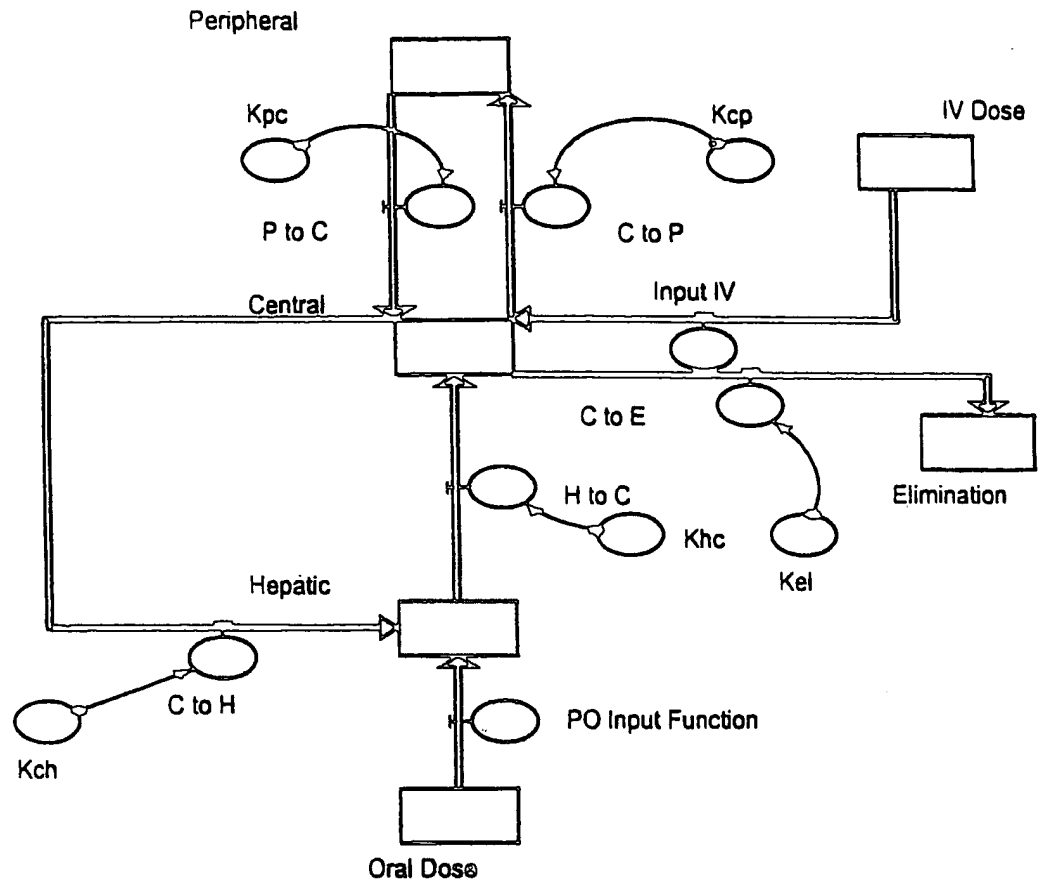


FIG. 19

RECEIVED

MAY 05 2003

TECH CENTER 1600/2900



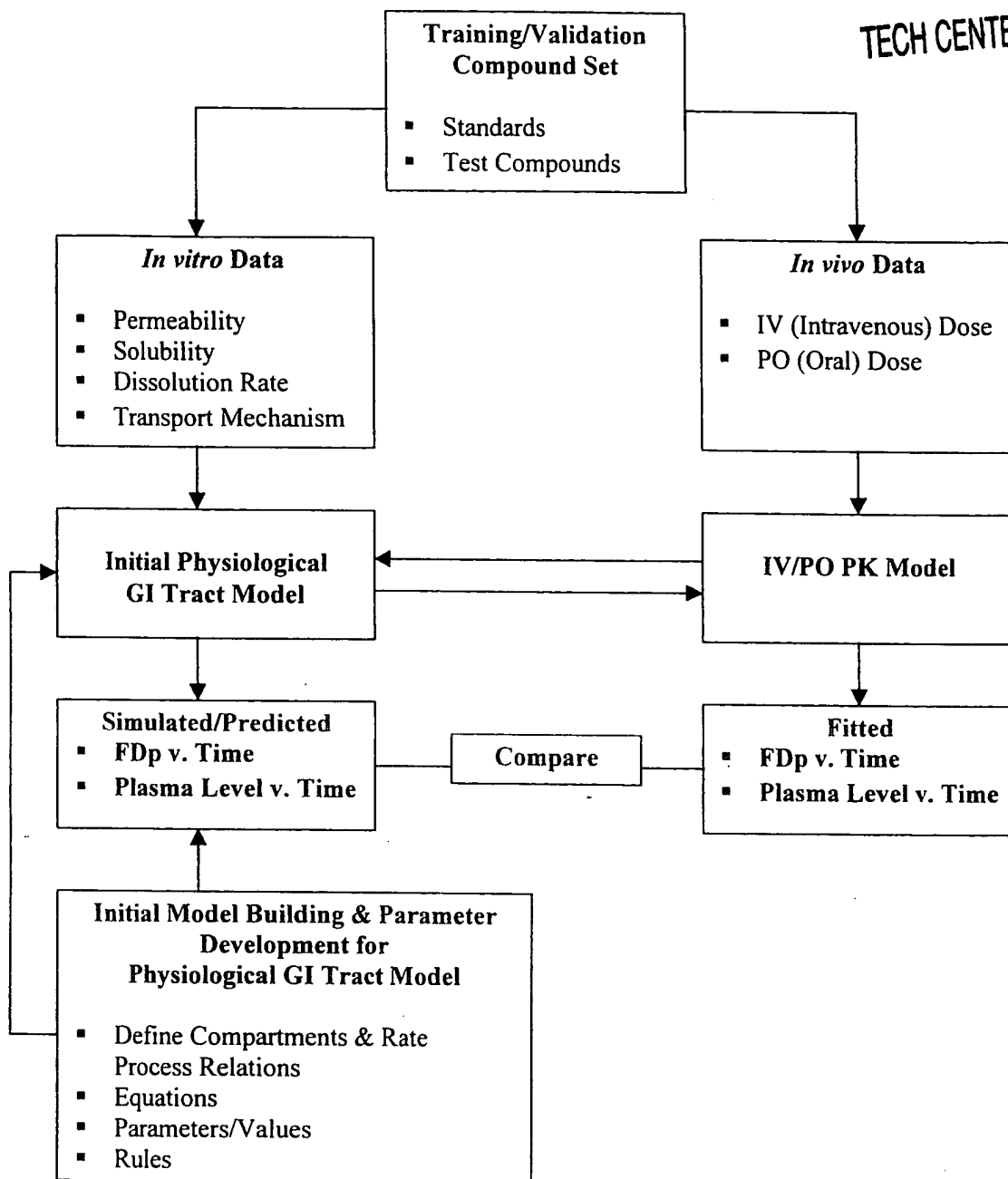


RECEIVED

MAY 05 2003

TECH CENTER 1600/2900

FIG. 20





RECEIVED

MAY 05 2003

TECH CENTER 1600/2900

FIG. 21

Gastrointestinal Transit

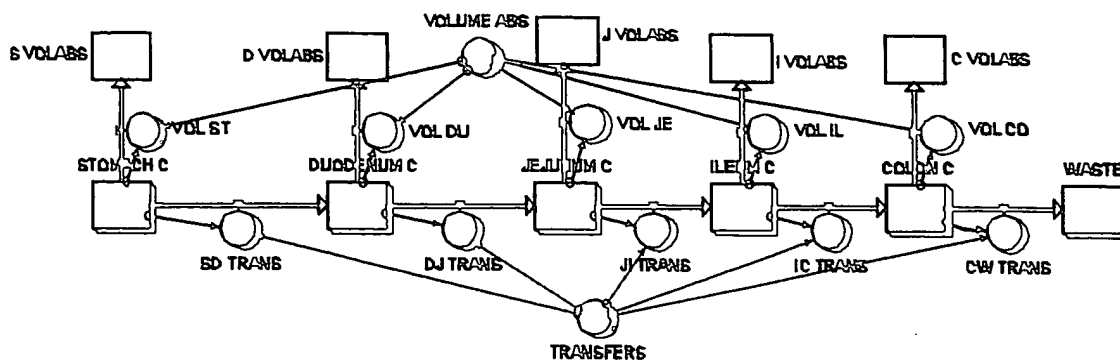
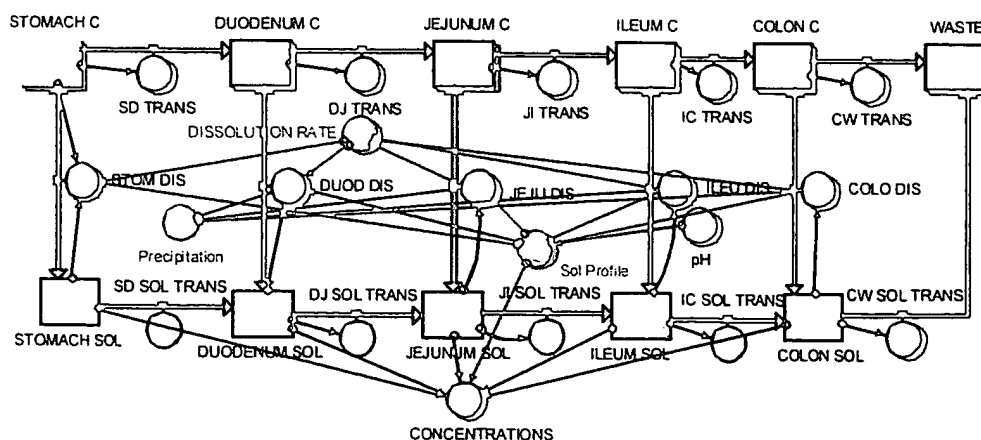


FIG. 22

pH Dependent Solubility and Dissolution





RECEIVED

MAY 05 2003

TECH CENTER 1600/2900

FIG. 23

Absorption

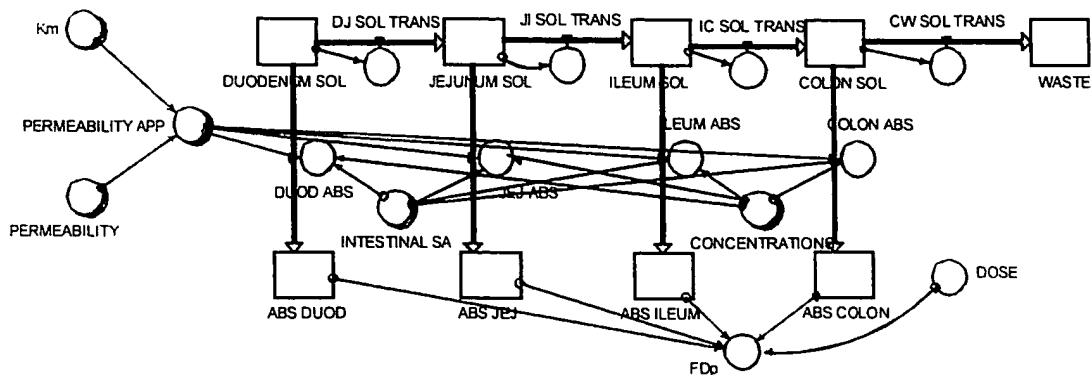
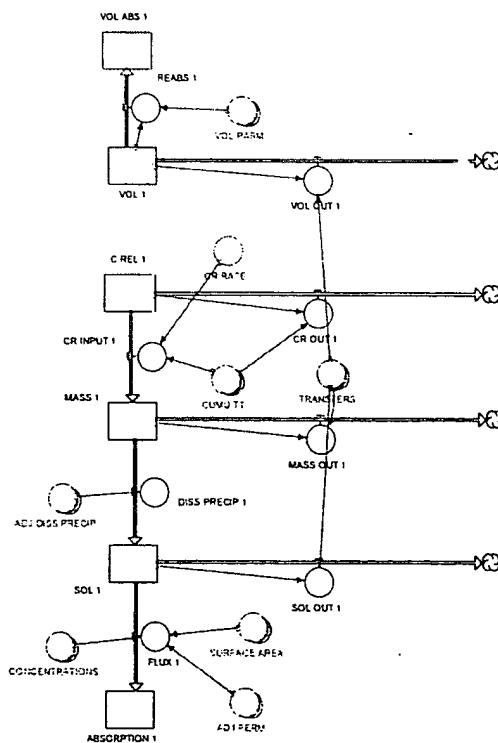


FIG. 24

GI Tract -Intestinal Model

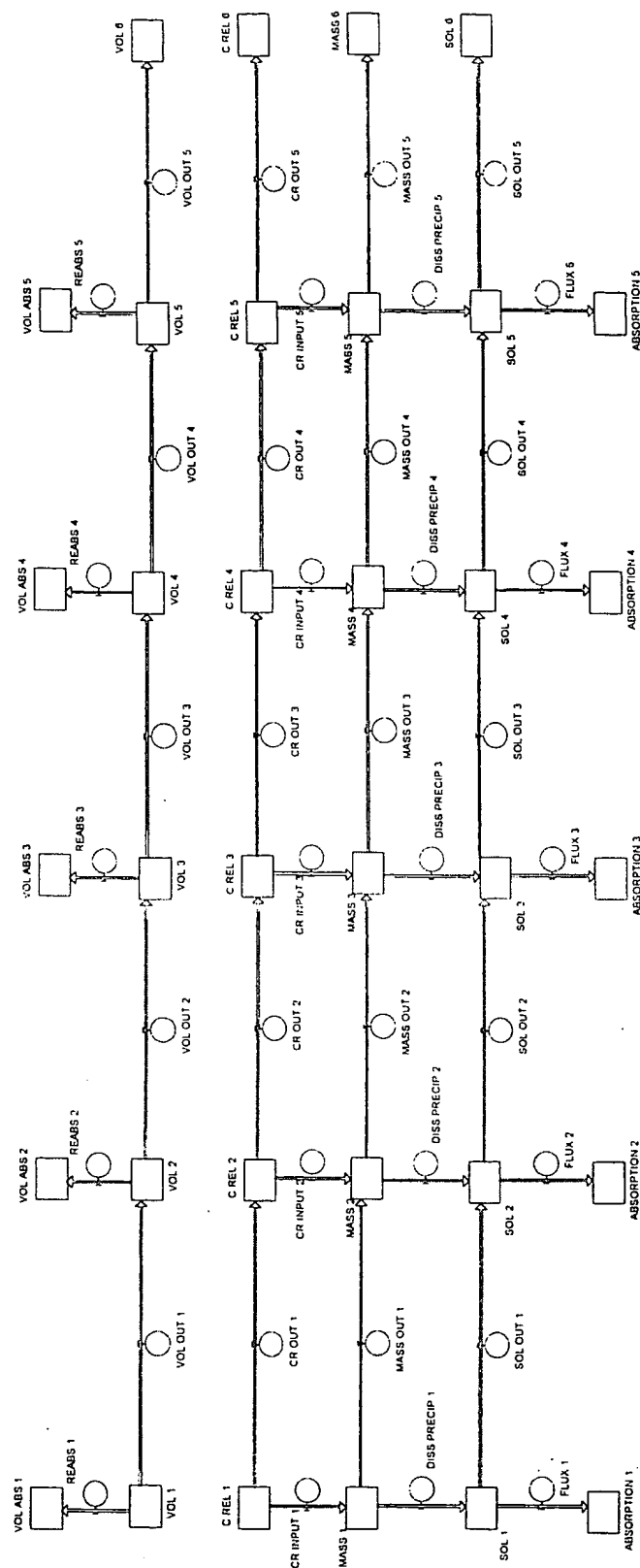




RECEIVED
MAY 05 2003
TECH CENTER 1600/2900

FIG. 25

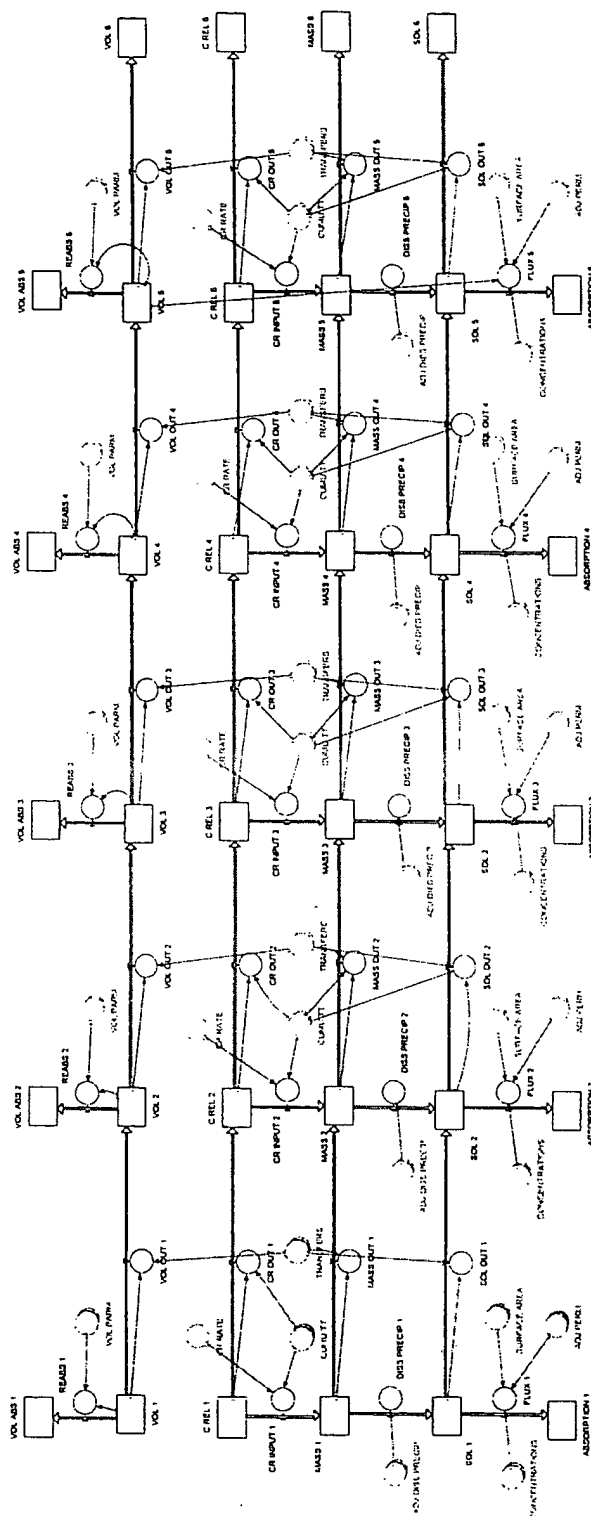
GI Tract-Intestinal Model (without converters, ghosts or connectors)





RECEIVED
MAY 05 2003
TECH CENTER 1600/2900

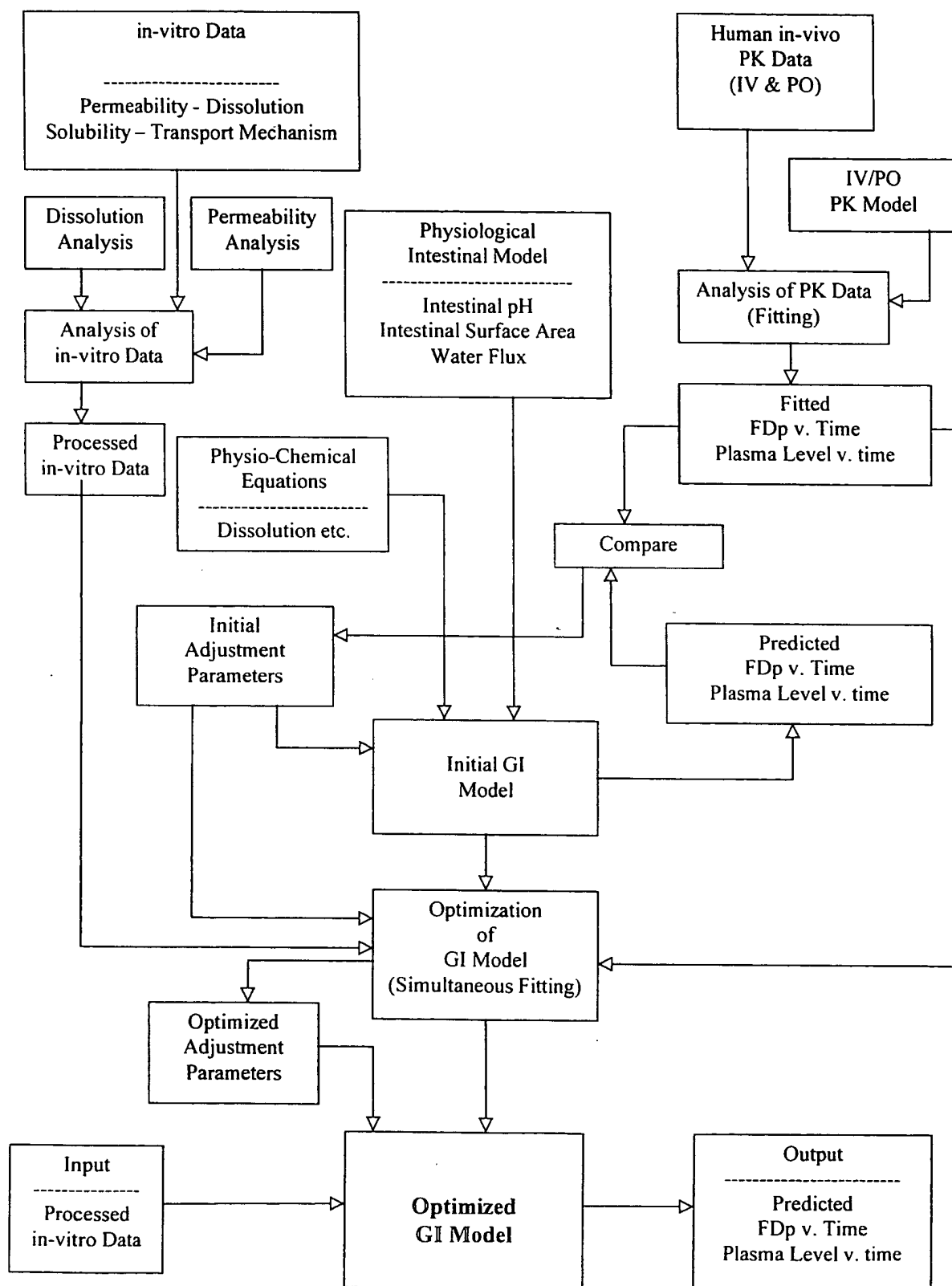
FIG. 26
GI Tract-Intestinal Model





RECEIVED
MAY 05 2003
TECH CENTER 1600/2900

FIG. 27





RECEIVED
MAY 05 2003
TECH CENTER 1600/2900

FIG. 28

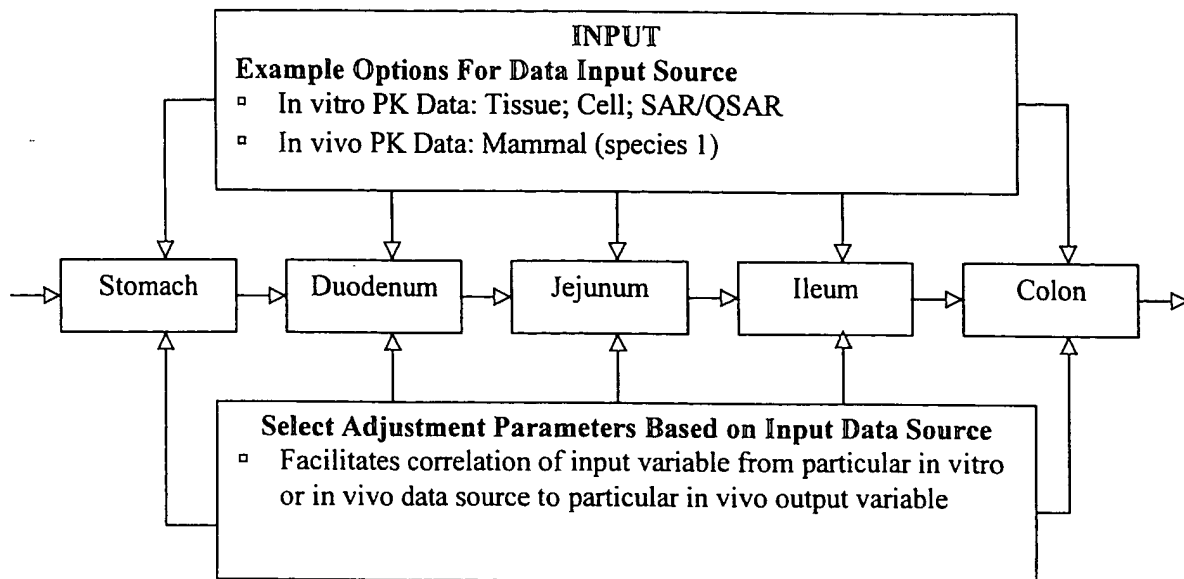
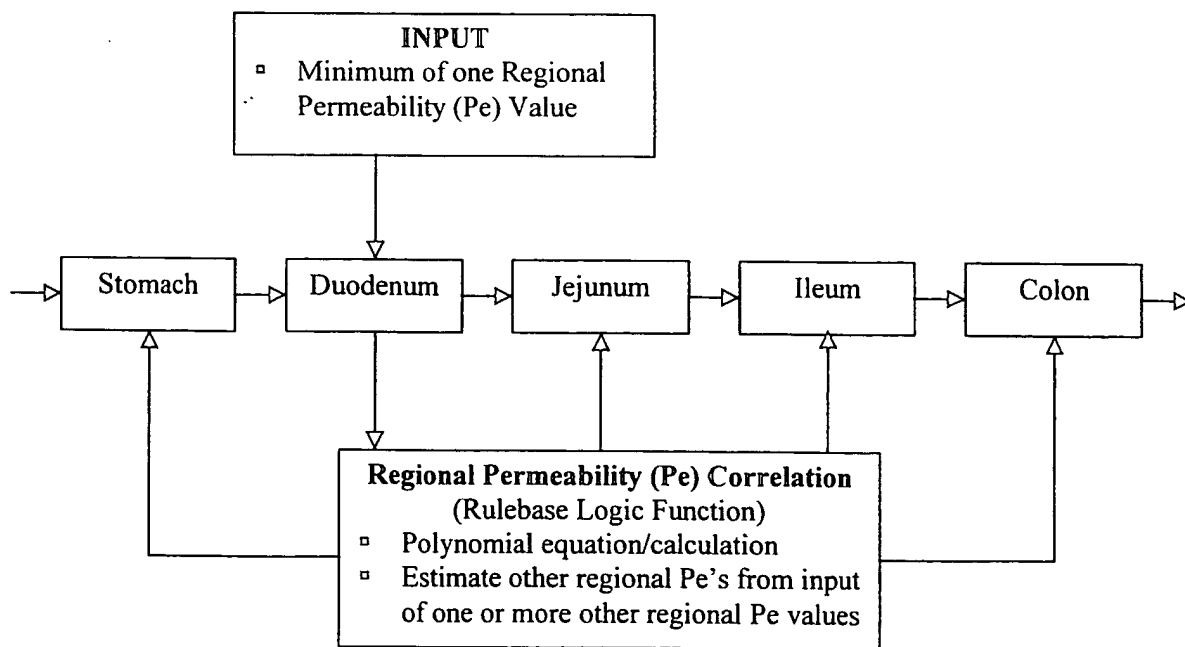


FIG. 29





RECEIVED

MAY 05 2003

TECH CENTER 1600/2900

FIG. 30

Parameters

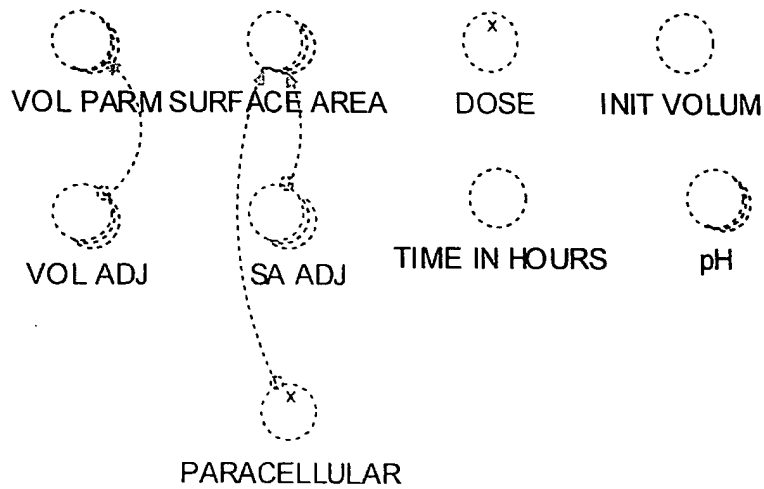
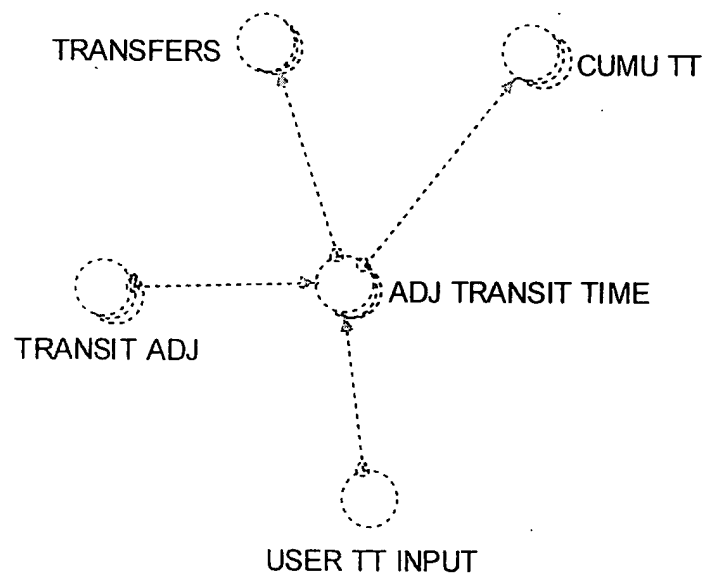


FIG. 31

Transit Time





RECEIVED
MAY 05 2003
TECH CENTER 1600/2900

FIG. 32

Permeability Calculation

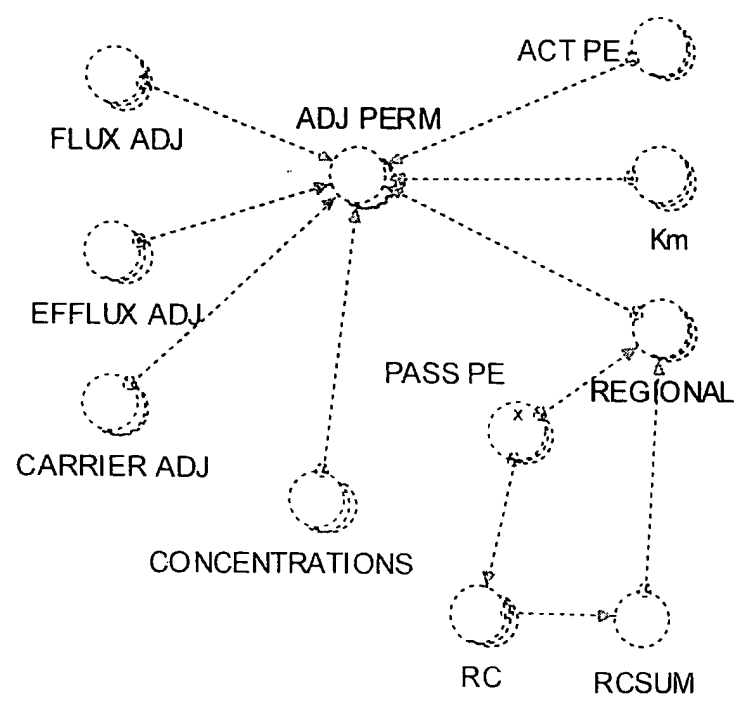
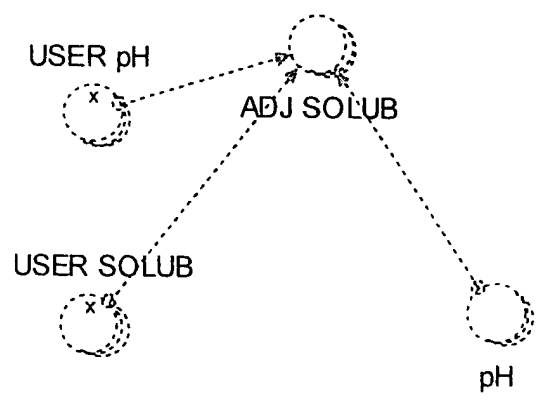


FIG. 33

Solubility Calculation





RECEIVED

MAY 05 2003

TECH CENTER 1600/2900

FIG. 34

Control Release Calculation

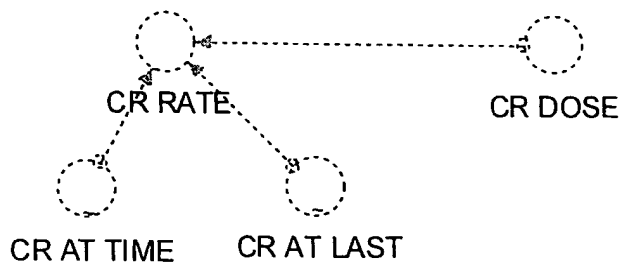
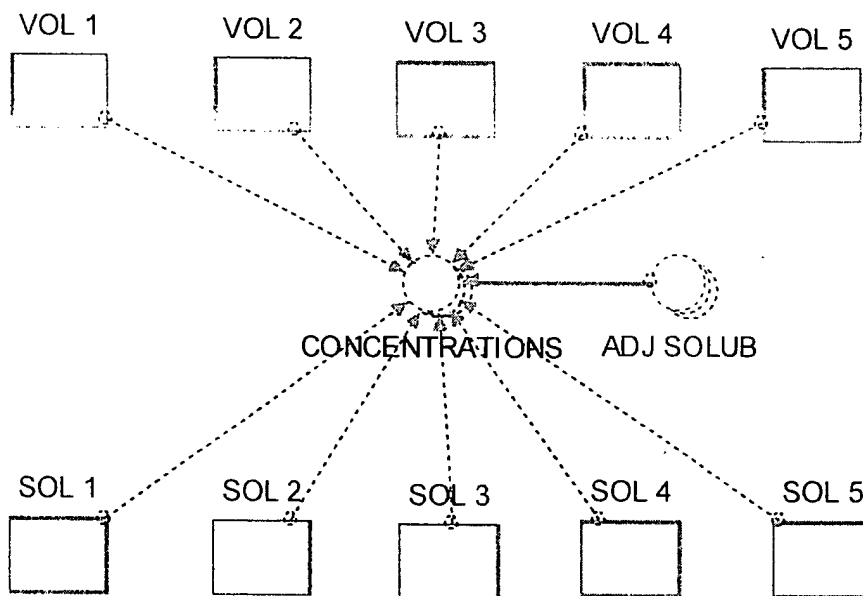


FIG. 35

Concentration Calculation





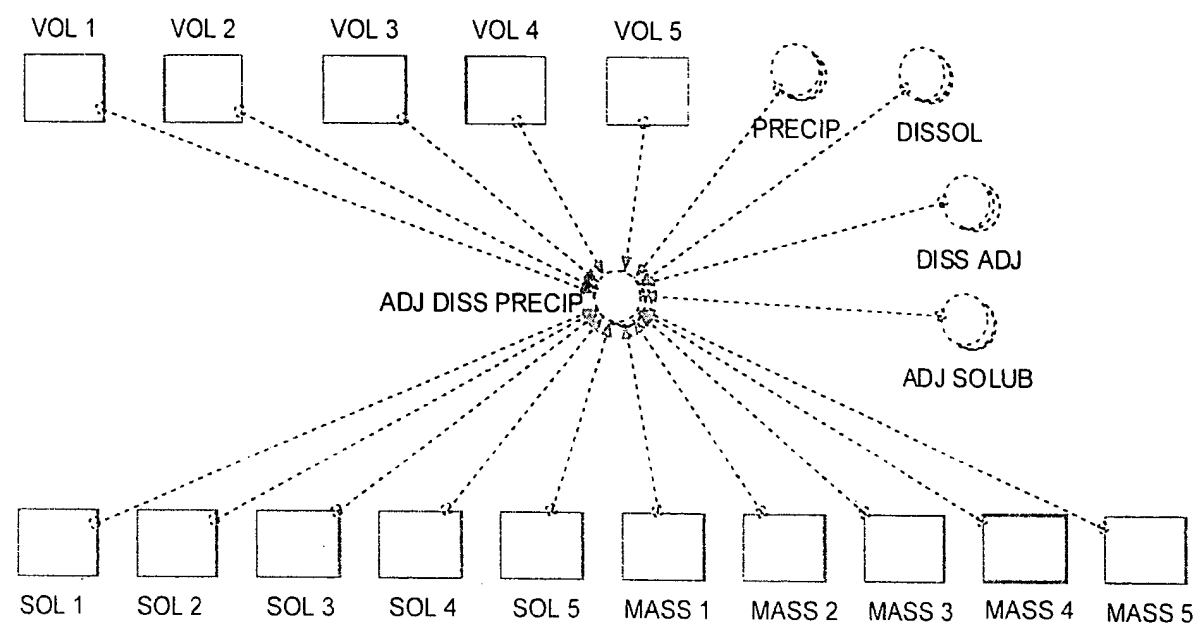
RECEIVED

MAY 05 2003

TECH CENTER 1600/2900

FIG. 36

Dissolution Calculation





RECEIVED
MAY 05 2003
TECH CENTER 1600/2900

FIG. 37

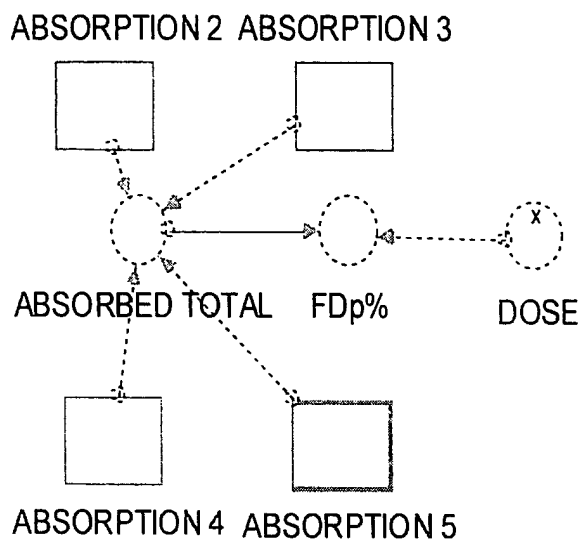
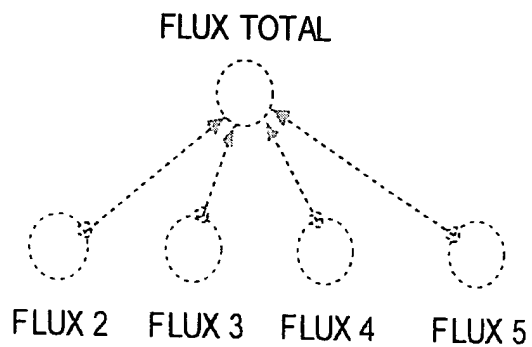


FIG. 38





RECEIVED

MAY 05 2003

TECH CENTER 1600/2900

FIG. 39

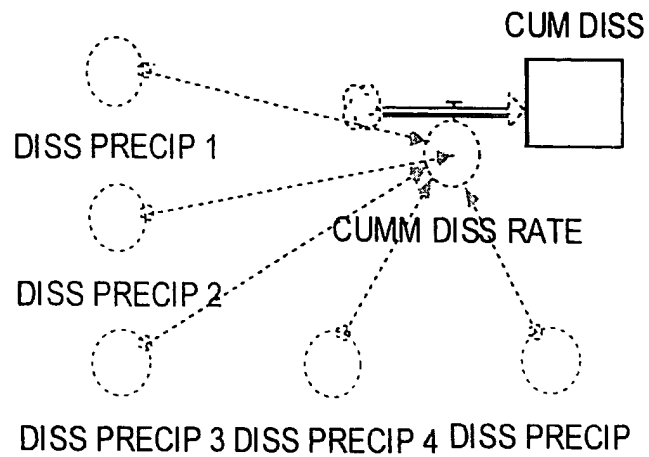
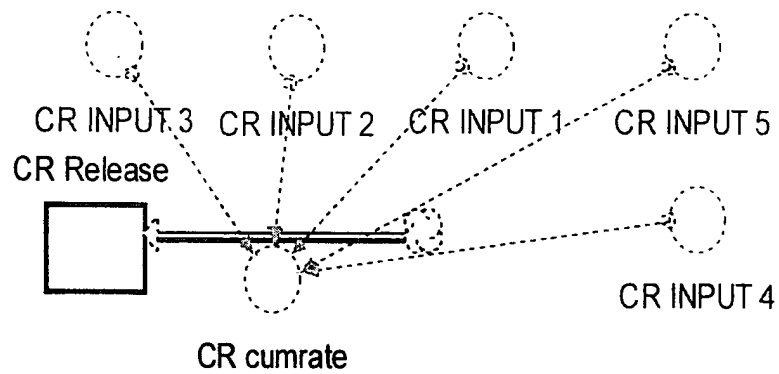


FIG. 40





RECEIVED

MAY 05 2003

TECH CENTER 1600/2900

FIG. 41

Physiological GI Tract Model

Database

- **GI Segment Compartments**
 - Fluid Absorption
 - Fluid Volume
 - Insoluble Mass
 - Soluble Mass
 - Soluble Mass Absorption
 - Dosage Form Mass
- **GI Segment Flow Regulators**
 - Fluid Absorption Rate
 - Fluid Volume Transit Rate
 - Insoluble Mass Transit Rate
 - Insoluble Mass Dissolution Rate
 - Soluble Mass Transit Rate
 - Soluble Mass Absorption Rate
 - Dosage Form Disintegration/Release Rate
- **GI Segment Converters**
 - Fluid Volume Absorption Rate Constant
 - GI Transit Rate Constant
 - Adjusted Dissolution Rate Constant
 - Dissolved Drug Concentration
 - Adjusted Surface Area
 - Adjusted Permeability

Rulebase

- GI Transit
- Dissolution
- Absorption
- Permeability Calculations
- Concentration Calculations
- Computational Error Corrections



RECEIVED

MAY 05 2003

TECH CENTER 1600/2900

FIG. 42

Physiological GI Tract Model

- **GI Segment Compartments & Flow Regulators**
 - **Fluid Absorption**
 - *Fluid Absorption Rate*
 - **Fluid Volume**
 - *Fluid Volume Absorption Rate*
 - *Fluid Volume Transit Rate*
 - **Insoluble Mass**
 - *Insoluble Mass Transit Rate*
 - *Insoluble Mass Dissolution Rate*
 - **Soluble Mass**
 - *Insoluble Mass Dissolution Rate*
 - *Soluble Mass Transit Rate*
 - *Soluble Mass Absorption Rate*
 - **Soluble Mass Absorption**
 - *Soluble Mass Absorption Rate*

FIG. 43

Physiological GI Tract Model

- **GI Segments Flow Regulators & Converters**
 - **Fluid Absorption Rate**
 - *Fluid Volume*
 - *Fluid Volume Absorption Rate Constant*
 - **Fluid Volume Transit Rate**
 - *Fluid Volume*
 - *Fluid Volume Transit Rate Constant*
 - **Insoluble Mass Transit Rate**
 - *Insoluble Mass*
 - *Insoluble Mass Transit Rate Constant*
 - **Insoluble Mass Dissolution Rate**
 - *Insoluble Mass*
 - *Dissolution Rate Constant*
 - **Soluble Mass Transit Rate**
 - *Soluble Mass*
 - *Soluble Mass Transit Rate Constant*
 - **Soluble Mass Absorption Rate (Flux)**
 - *Surface Area*
 - *Dissolved Mass Concentration*
 - *Permeability*



RECEIVED

MAY 05 2003

TECH CENTER 1600/2900

FIG. 44

Physiological GI Tract Model

- **Converters**
 - **Permeability**
 - Passive Absorption Adjustment Parameter
 - Efflux/Secretion Adjustment Parameter
 - Active Absorption Adjustment Parameter
 - Active or Carrier Mediated Absorptive Permeability
 - Km
 - Passive Permeability/Regional Correlation
 - Passive Permeability
 - Logic Function For Regional Correlation
 - Passive Permeability
 - Logic Function For Regional Correlation
 - Dissolved Mass Concentrations
 - **Dissolved Mass Concentration**
 - Fluid Volume
 - Solubility
 - pH
 - Solubility
 - **Dissolution Rate Constant**
 - Fluid Volume
 - Precipitation Rate Constant
 - Dissolution Rate Adjustment Parameter
 - Solubility
 - Insoluble Mass
 - Soluble Mass
 - **Surface Area**
 - Surface Area Adjustment Parameter
 - Transport Mechanism
 - **Transit Rate**
 - Transit Time Adjustment Parameter
 - User Adjusted Transit Time
 - **Fluid Volume Absorption Rate Constant**
 - Fluid Volume Adjustment Parameter



MAY 10 2003

TECH CENTER 1600/2900

FIG. 45

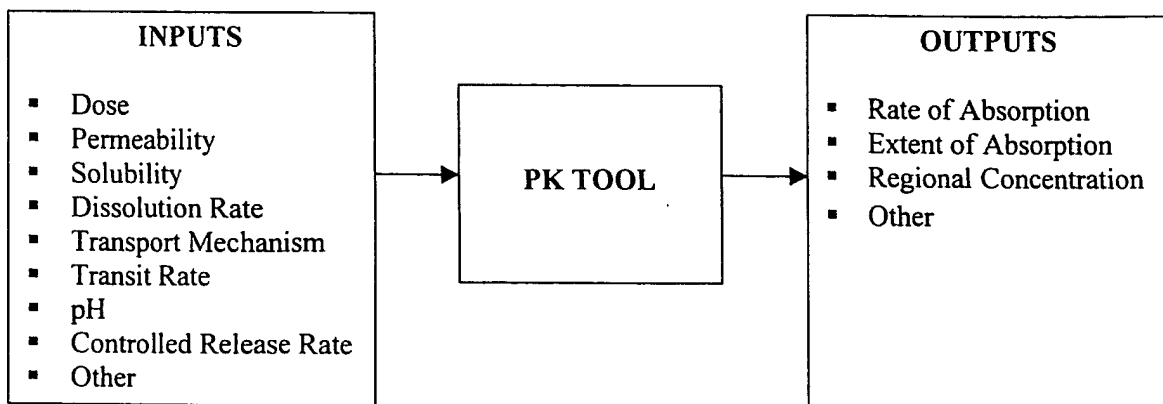
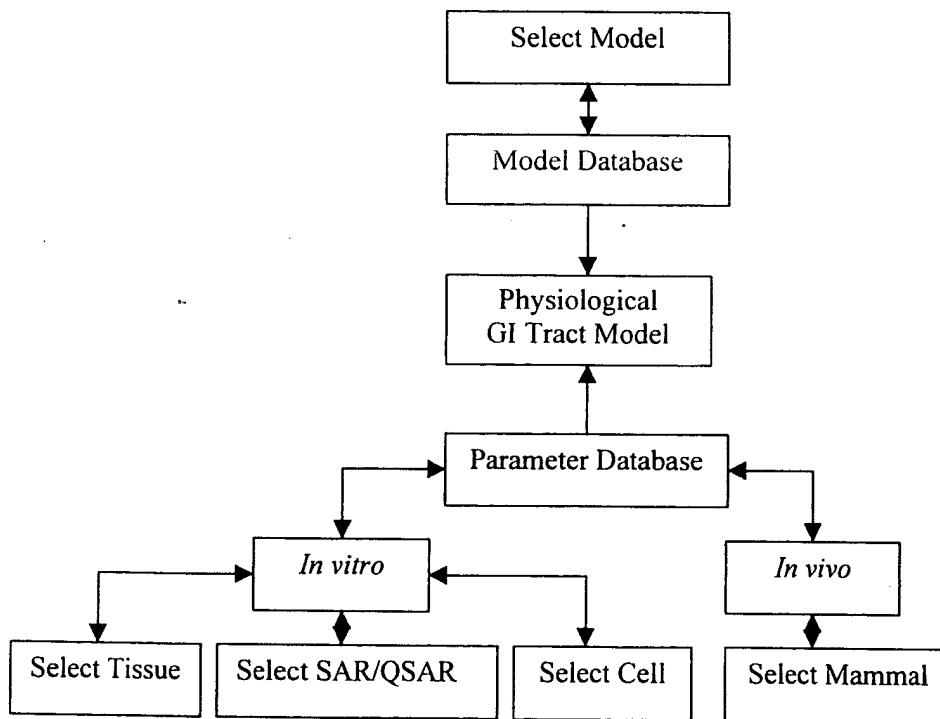


FIG. 46



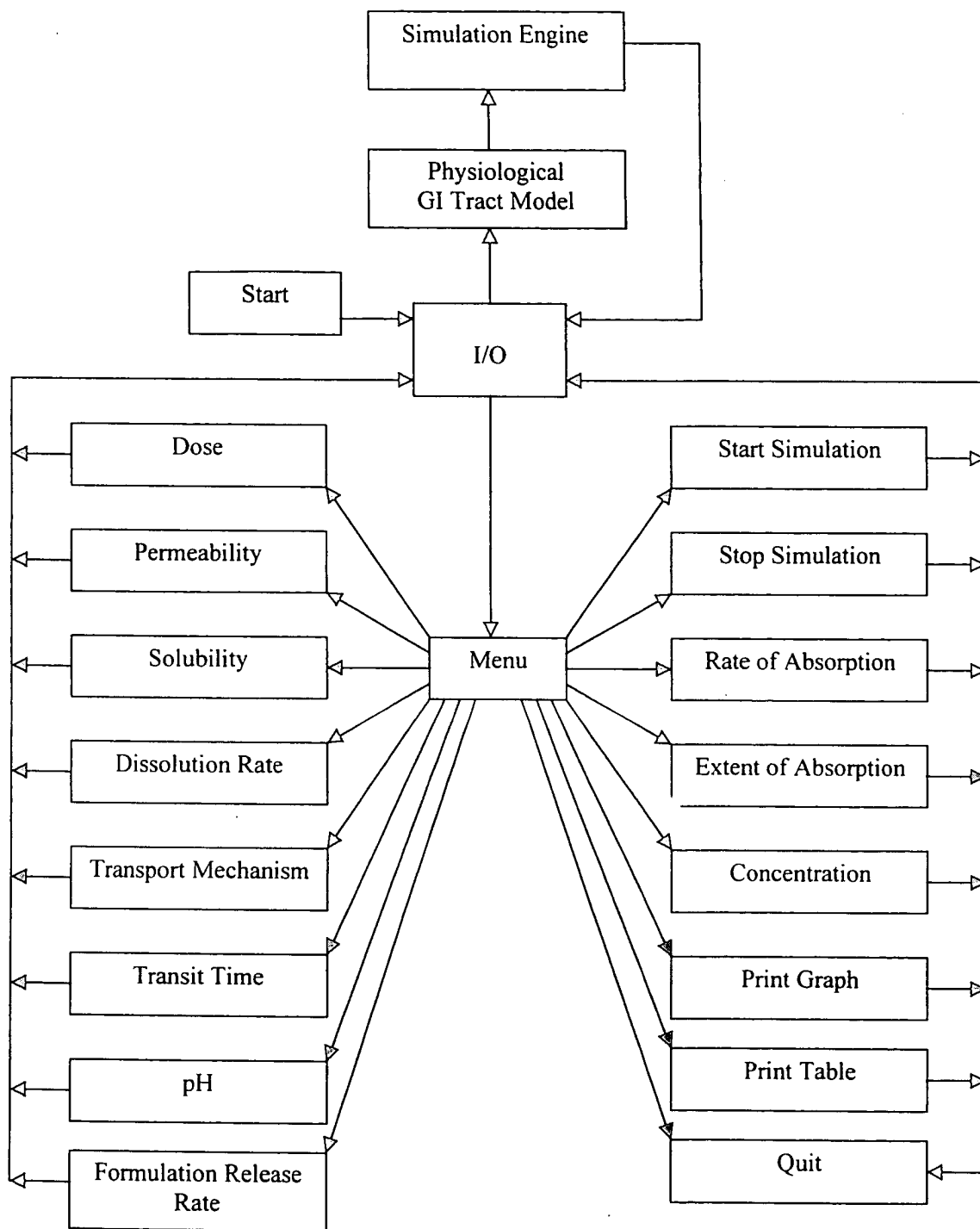


RECEIVED

MAY 05 2003

TECH CENTER 1600/2900

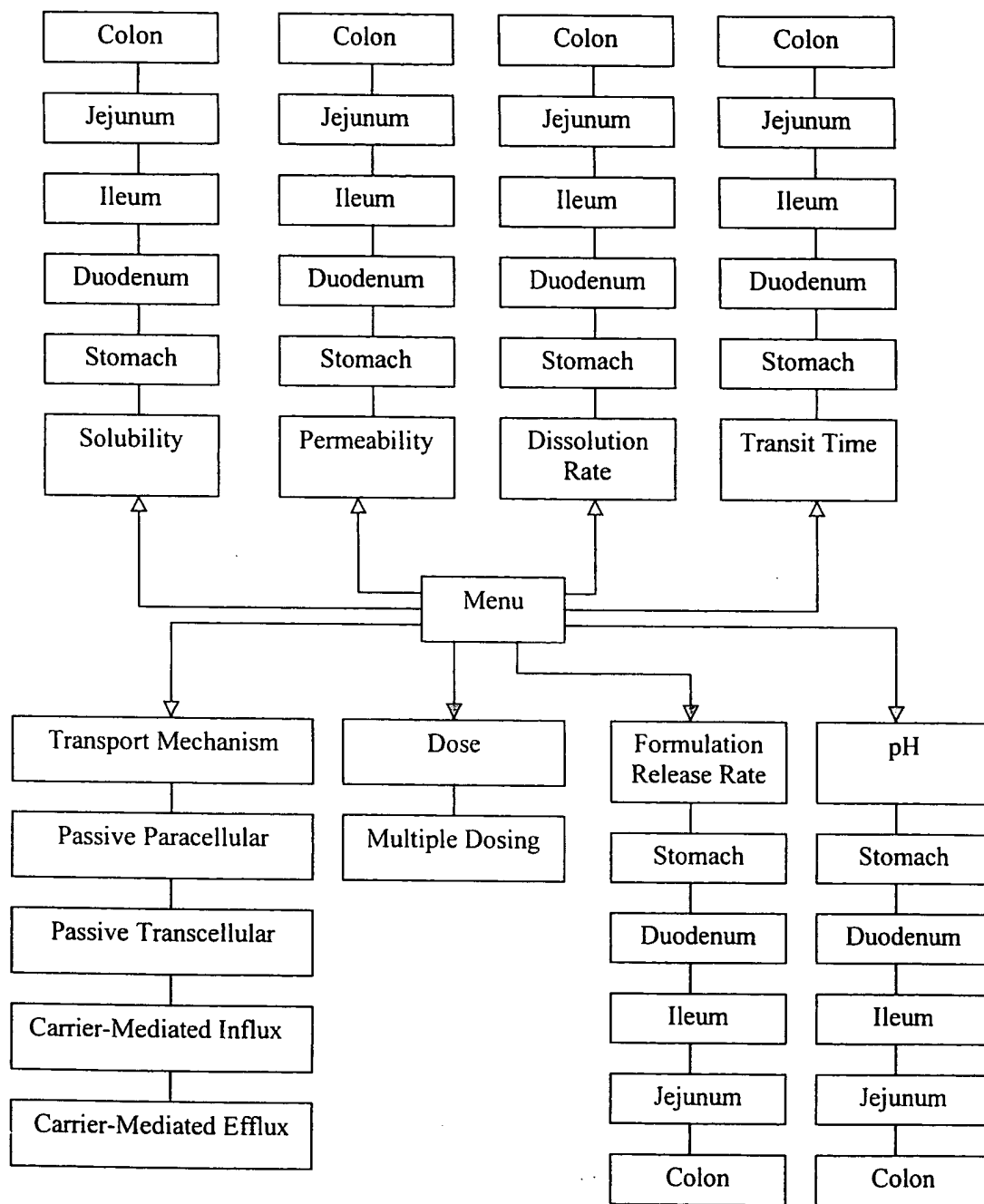
FIG. 47





RECEIVED
MAY 05 2003
TECH CENTER 1600/2900

FIG. 48





RECEIVED

MAY 05 2003

TECH CENTER 1600/2900

FIG. 49

Correlation of FDp Extent - GI Model and Pharmacokinetic data

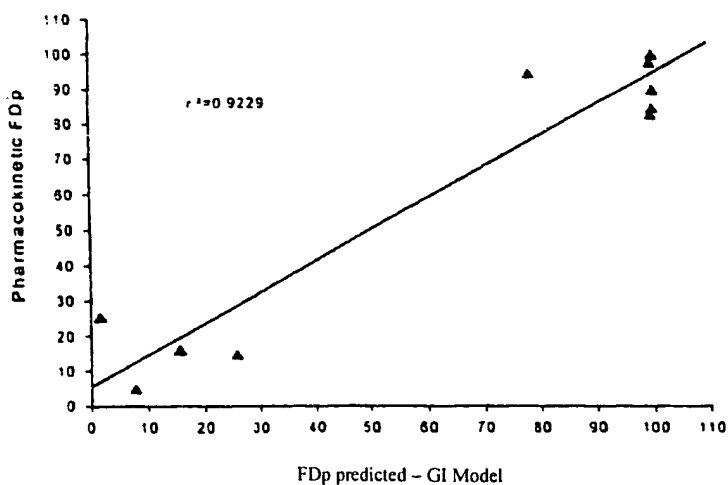
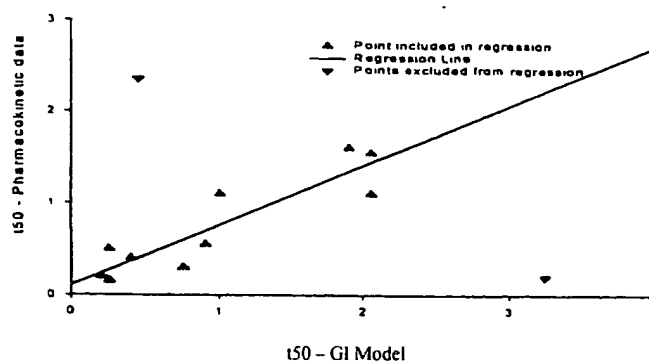


FIG. 50

Correlation of FDp rate of absorption - GI Model and Pharmacokinetic Data





RECEIVED

MAY 05 2003

TECH CENTER 1600/2900

FIG. 51

PO Pharmacokinetic Data
Compound α 1

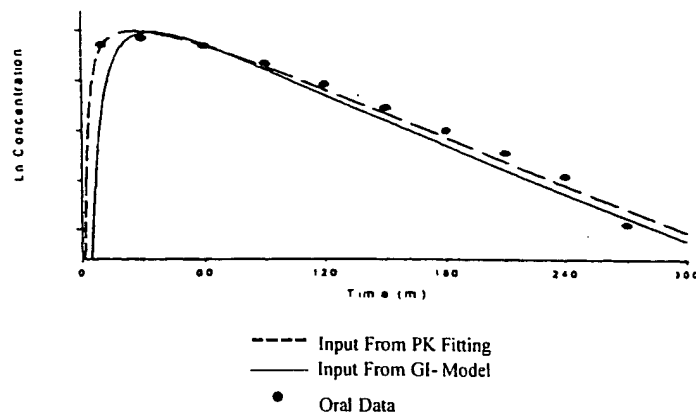
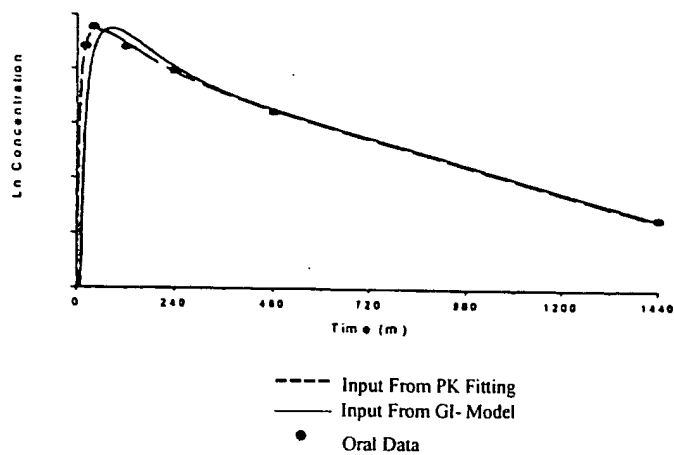


FIG. 52

PO Pharmacokinetic Data
Compound α 4





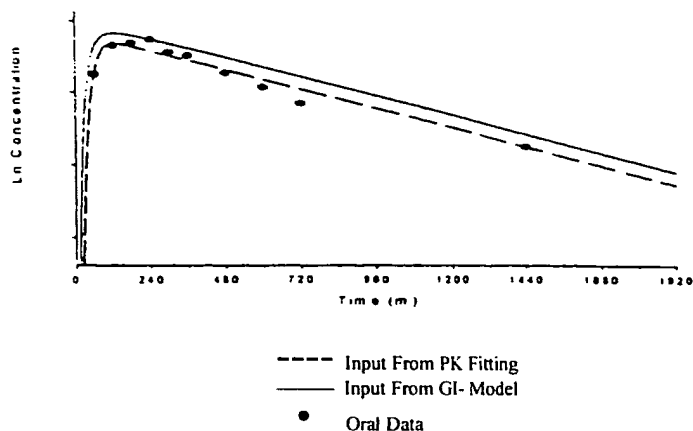
RECEIVED

MAY 05 2003

TECH CENTER 1600/2900

FIG. 53

PO Pharmacokinetic Data
Compound β 6





RECEIVED

MAY 05 2003

TECH CENTER 1600/2900

FIG. 54

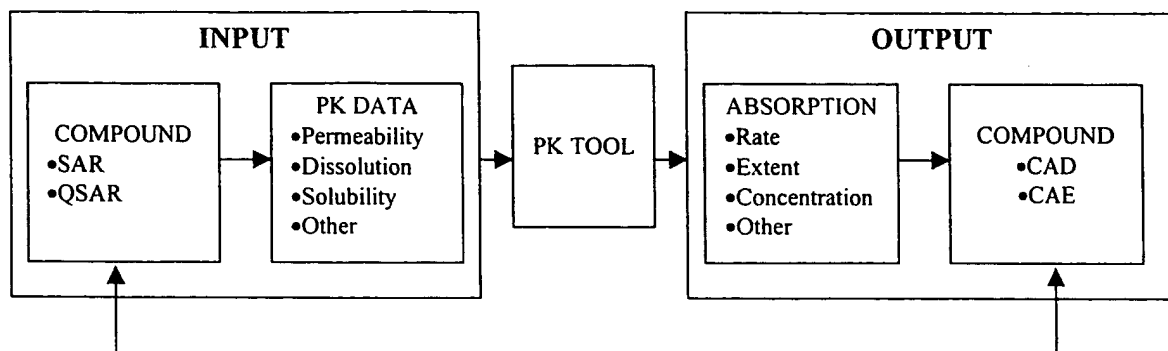


FIG. 55

